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Isolated Valvular Pulmonic Stenosis

Clinical and Physiologic Response to Open Valvuloplasty

By S. Gilbert Blount, Jr., M.D., Malcolm C. McCord, M.D., Helmut Mueller, M.D., and Henry Swan, M.D.

The preoperative and postoperative clinical and physiologic data are presented in 10 patients with isolated valvular pulmonic stenosis. The valvulotomy was performed in five patients by the generally accepted blind ventricular approach, while in the remaining five patients the valvular surgery was accomplished by a direct pulmonary arterial approach. The physiologic data revealed uniform obliteration of the systolic pressure gradient from the right ventricle to the pulmonary artery in the patients operated by the direct technic in striking contrast to the inadequate and variable relief of stenosis by the transventricular approach.

ISOLATED valvular pulmonic stenosis has been recognized in recent years to be a relatively common congenital anomaly. It has also become evident during this period that it is not the benign lesion that the asymptomatic clinical picture might suggest.[1] Whenever the clinical diagnosis of valvular pulmonic stenosis with intact ventricular septum is entertained, complete physiologic evaluation is advisable and operative intervention should be considered in every instance. Sellors[2] initiated operative correction of this lesion in 1948, employing a transventricular approach. This approach has subsequently been developed by Brock[3] and others[4, 5] and employed in a large number of patients. While subjective clinical improvement has been reported, studies comparing the preoperative and postoperative physiologic status of such patients have been infrequent. The few reported studies of postoperative physiologic changes have demonstrated inadequate relief of the pulmonic valve obstruction in most instances and have been characterized by a striking lack of uniformity[6-11] (table 1).

A transarterial approach to the pulmonic valve has been previously reported,[12] but has been largely abandoned because of technical problems relating to the blind approach existing with closed heart surgery. Thus at the present time the transventricular approach to the stenotic valve is almost universally employed.

The recent application of hypothermia to this problem[13] has allowed open heart surgery, and under these conditions the stenotic valve may be viewed with deliberation and valvuloplasty performed. This present communication deals with the clinical and physiologic response to transarterial pulmonic valvuloplasty and compares the results obtained by this method with those obtained following the transventricular approach.

Material and Methods

A diagnosis of isolated valvular pulmonic stenosis has been established in 51 patients during the past three years at this institution. Surgical therapy has been recommended in all patients demonstrating right ventricular systolic pressures exceeding 75 mm. Hg. Operative therapy was accepted and car-

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TABLE 1.—*Summary of Published Data of Postoperative Hemodynamic Changes Following Transventricular Pulmonic Valvuloplasty*

Source	Number of Cases	Pre-op. Average Rt. Vent. Pressure	Post-op. Average Rt. Vent. Pressure	Decrease Rt. Vent. Pressure (mm. Hg)	Decrease Rt. Vent. Pressure in %
Lurie and Schumaker	7	99/−1	78/−2	21	30
Bing, et al.	8	127/29	92/16	35	36
Kirklin, et al.	2	125/5	52/6	73	77
Galligan, et al.	2	179/5	59/3	120	81
Soulie, et al.	9	171/7	108/6	63	45
Humphreys, et al.	3	193/12	75/10	118	72
Blount, et al. (Present communications)	5	168/2	65/1	103	75

ried out in 15 patients. Prior to 1953 the valvulotomy was performed by the ventricular approach, the Brock technic. This method consisted of incision of the right ventricular wall in the outflow area, and blind valvulotomy, using a valvulotome followed by dilatation of the sectioned pulmonic valve. Pulmonary valvulotomy was performed by this method in eight patients with an operative fatality in two patients. Postoperative catheterization data were obtained a year or more following surgery in five of these patients. For convenience this group will be designated as group A in the following presentation.

A pulmonary arterial approach was adopted in 1953 for the surgical correction of valvular pulmonic stenosis.[14] Briefly this method consists of the use of hypothermia with occlusion of circulation. The pulmonary artery is incised and the pulmonic valve is exposed to direct vision. The stenosis is relieved by incision or partial excision as indicated in each instance. This operative procedure has been carried out in seven patients with no operative fatalities. Preoperative and postoperative physiologic studies were obtained in five consecutive patients. These five patients compose group B in the following presentation.

RESULTS

Clinical Observations

Three of the five patients operated by the Brock technic, group A, were symptomatic, describing varying degrees of limitation of exercise tolerance. Each of these patients was cyanotic. All three patients described an improvement in symptoms following surgery, and there was an apparent decrease in the degree of cyanosis. One patient in the group operated by the pulmonary arterial approach, group B, was limited in exercise tolerance and was slightly cyanotic. This patient showed an improvement in exercise tolerance postoperatively. The remaining patients in both groups were asymptomatic.

The pertinent findings on physical examination involved cardiac murmurs. The intensity of the systolic murmur in the second left intercostal space was grade IV or more in all patients in both groups preoperatively, and a thrill was palpable in the left second intercostal space in all patients. In group A the intensity of the systolic murmur decreased following surgery in all instances but one, C. T., where the intensity remained grade V. The magnitude of this decrease was only moderate, the murmur being at least grade III in intensity in the remaining patients, and a thrill persisting in three patients. In group B the murmur decreased to grade II in all instances and the thrill disappeared in all patients.

One of the patients in group A developed a diastolic murmur along the left sternal border following surgery. A diastolic murmur appeared in this location postoperatively in four of the five patients in group B. This murmur was medium to low in pitch and somewhat rough in quality, and was of maximum intensity in the third left intercostal space. The intensity

TABLE 2.—*Magnitude of Decrease in Amplitude of R Wave in Precordial Lead V_1. The First Five Patients Comprise Group A While the Second Five Represent Group B*

Patient	Pre-op. R-V_1	Post-op.	
		R-V_1	Time after surgery
C. T.	31	12	2½ yrs.
R. M.	36	24	1 yr.
D. N.	24	7	11 mos.
D. L.	20	9	6 mos.
A. N.	2	3	1 yr.
R. H.	19	16	8 mos.
J. K.	30	10	9 mos.
G. S.	25	9	10 mos.
M. G.	13	5	5 mos.
D. M.	19	16	9 mos.

of this murmur varied from grade I to grade III.

The second heart sound in the second left intercostal space was decreased in intensity or absent prior to surgery in all patients. Postoperatively there was an increase in intensity or appearance of this sound in four of the patients in group A and in all of the patients in group B.

Electrocardiography

A tall R wave with a delayed intrinsicoid deflection time exceeding 0.03 second was present in precordial lead V_1 in 9 of the 10 patients preoperatively. Postoperatively there was a decrease in the amplitude of this R wave in lead V_1 in all nine patients (table 2). The average decrease in group A was 36 per cent whereas the average drop in the amplitude in group B was 42 per cent thus showing no significant difference. A significant change in the configuration of the QRS complex in lead V_1 was noted in three patients in group B. The high-amplitude R wave present preoperatively, indicating right ventricular hypertrophy, evolved to a lower amplitude rSR′

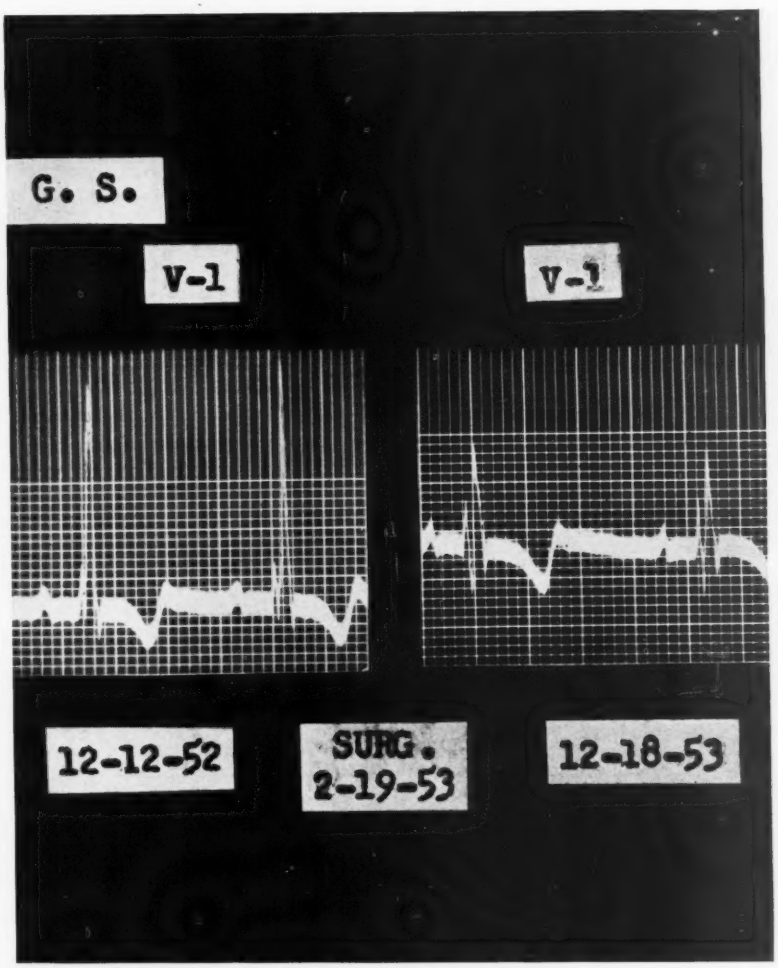

FIG. 1. Decrease in amplitude and appearance of a partial right bundle-branch block pattern following transarterial pulmonic valvuloplasty. (G. S. group B.)

pattern interpreted as incomplete or partial right bundle-branch block (fig. 1).

Roentgenography

The three patients in group A who were cyanotic showed a decreased vascularity of the peripheral lung fields prior to surgery. The vascularity was normal in the remaining patients in both groups. Following surgery there was no significant change in the peripheral vascularity of the lung fields in any patient.

The right and left pulmonary arteries showed a decreased amplitude of pulsation in all patients in both groups prior to surgery. In three patients in group A, those who were cyanotic, the low amplitude pulsations persisted after surgery. There was an increase in the pulsations in the remaining two patients. The amplitude of pulsations in the right pulmonary artery increased after surgery in all patients in group B.

There was no significant change in the prominence of the main pulmonary artery in any patient. The heart size increased following surgery in three patients in group A and in all patients in group B, the increase ranging from 0.5 to 1.5 cm. in transverse diameter (fig. 2). This increase in heart size occurred immediately following surgery, and there was no further significant change during the follow-up period (fig. 3).

Hemodynamics

The pressure phenomena observed in the right ventricle and pulmonary arteries in these patients is summarized in tables 3 and 4. In the five patients operated by the ventricular approach the right ventricular systolic pressure ranged from 110 to 221 mm. Hg with an average of 168 mm. Hg. The right ventricular systolic pressure was reduced following surgery in all patients in this group, the average postoperative pressure being 65 mm. Hg. This decrease ranged from 29 to 96 per cent with

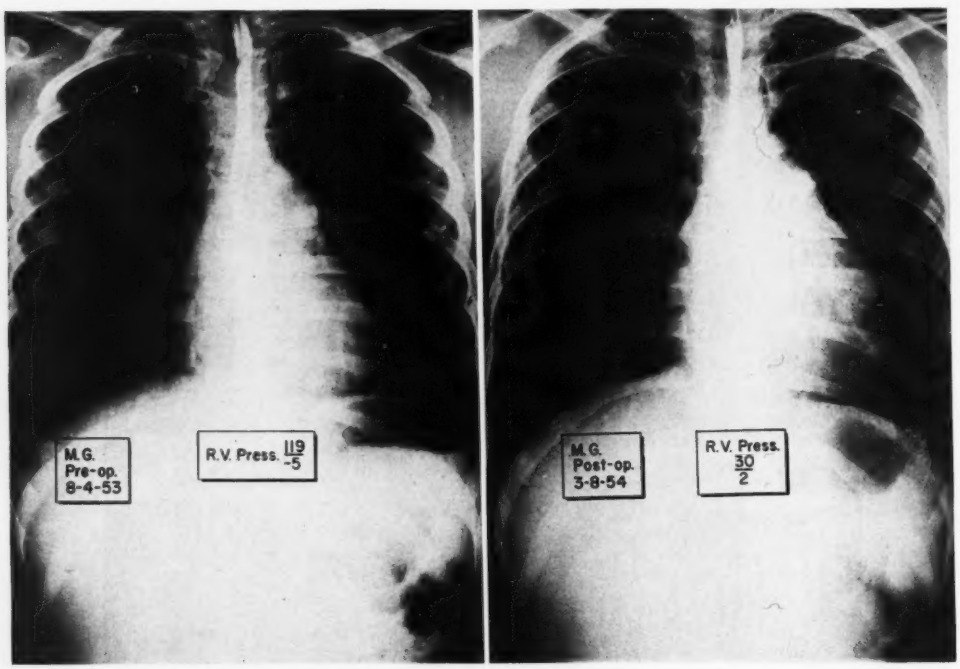

FIG. 2. Increase in transverse cardiac diameter and straightening of left cardiac border following transarterial pulmonic valvuloplasty. (M. G. group B.)

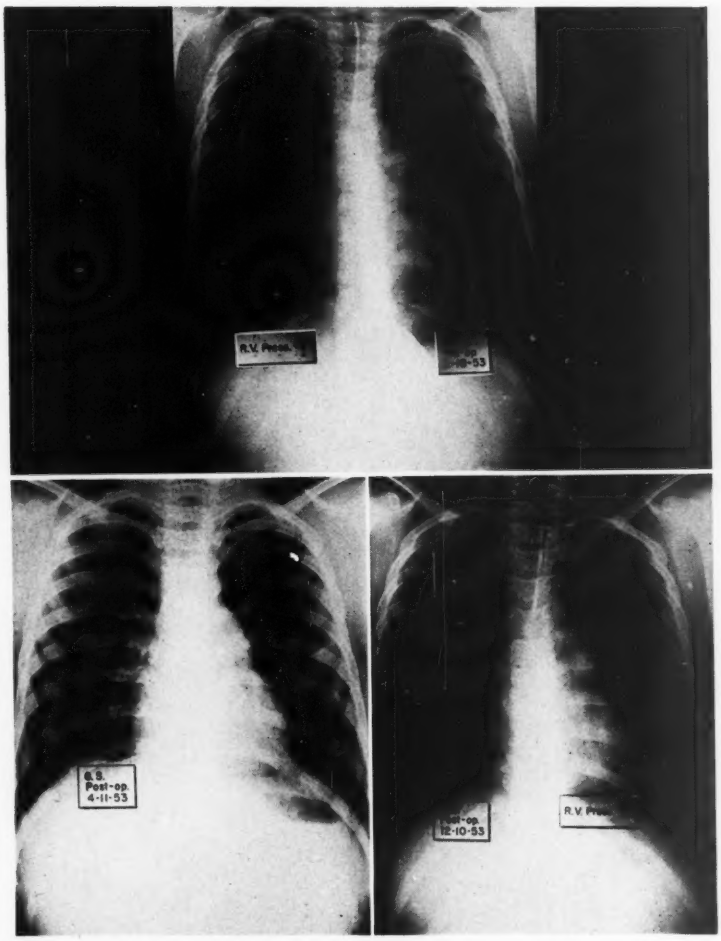

FIG. 3. Increase in heart size in immediate postoperative period with no progression during subsequent eight months. (G. S. group B.)

TABLE 3.—*Pressure Changes in the Right Ventricle and Pulmonary Artery Following Transventricular Pulmonic Valvuloplasty, Group A*

Patient	Pre.-op.		Post-op.		Decrease Rt. Vent. Pressure (mm. Hg)	Decrease Rt. Vent. Pressure in %
	Rt. Vent.	Pulm. Art.	Rt. Vent.	Pulm. Art.		
C. T.	200/5	20/16	151/1	22/13	49	29
R. M.	166/−7	13/8	38/2	25/10	128	94
D. N.	221/10	18/11	60/6	35/10	161	84
D. L.	142/−1	13/6	34/5	14/8	108	96
A. N.	110/3	16/7	40/2	14/9	70	87
Avg.	168/2	16/10	65/3	22/10	103	75

TABLE 4.—*Pressure Changes in the Right Ventricle and Pulmonary Artery Following Transarterial Pulmonic Valvuloplasty, Group B*

Patient	Pre-op.		Post-op.		Decrease Rt. Vent. Pressure (mm. Hg)	Decrease Rt. Vent. Pressure in %
	R. V.	P. A.	R. V.	P. A.		
R. H.	93/3	23/12	29/0	23/8	64	100
J. K.	142/−2	17/7	19/−5	15/3	123	100
G. S.	110/3	18/12	32/−1	32/9	78	98
M. G.	119/−5	18/9	29/7	25/9	89	100
D. M.	115/54	—	29/7	15/9	86	100
Avg.	116/11	19/10	28/1	23/7	88	100

an average reduction of 75 per cent. This value was derived by a comparison of the preoperative right ventricular systolic pressure with a theoretic normal of 30 mm. Hg and calculated as follows:

$$\frac{\textit{Decrease in RV systolic pressure}}{\textit{Preoperative RV systolic pressure—30 mm. Hg}} \times 100$$

The pulmonary arterial pressures in group A were uniformly low preoperatively, averaging 16/10 mm. Hg. A normal pulmonary artery pulse pressure was approximated following surgery in only two of the five patients in group A (fig. 4) while in the remaining three patients a narrow pulse pressure persisted (fig. 5). The average postoperative pulmonary artery pressure in this group was 22/10 mm. Hg. In all patients a pressure gradient between the right ventricle and the pulmonary artery during systole persisted following surgery, averaging 43 mm. Hg. There was thus evidence of residual stenosis at the pulmonic valve level in every patient in group A.

The right ventricular systolic pressure in the patients operated by the pulmonary arterial route ranged from 93 to 142 mm. Hg, with an average of 116 mm. Hg. Following operation the right ventricular pressure was reduced to normal levels in every instance with an average pressure of 28 mm. Hg.

The pulmonary arterial pressure was low, and there was a narrow pulse pressure in every patient preoperatively with an average pulmonary artery pressure of 19/10 mm. Hg. Following surgery the pulse pressure increased in all patients, and a normal pulmonary

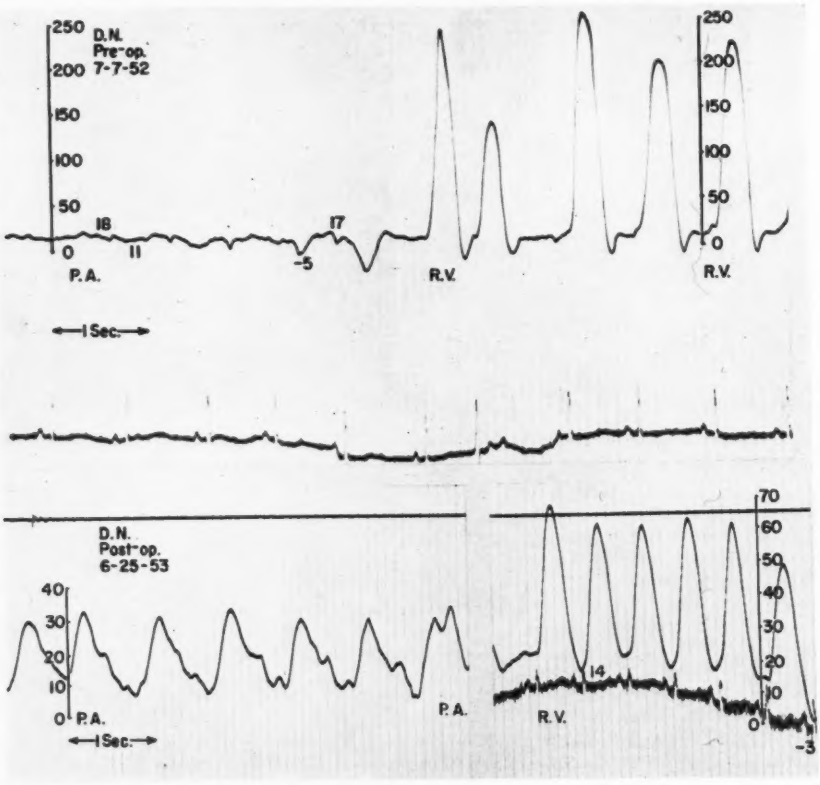

FIG. 4. Reduction of right ventricular pressure and return to normal of pulmonary arterial pressure and pulse contour following transventricular valvulotomy. (D. N. group A.)

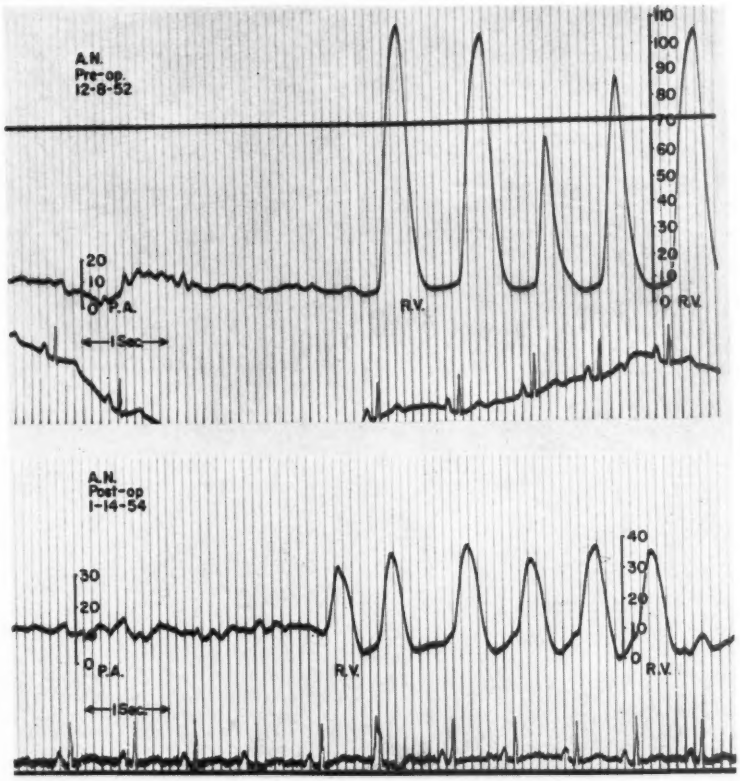

FIG. 5. Reduction in right ventricular pressure to near normal levels and persistence of low-pressure pulmonary arterial pulse wave following transventricular valvulotomy. (A. N., group A.)

arterial pulse contour was established (figs. 6 and 7).

The most striking physiologic change was the almost complete obliteration of the systolic pressure gradient between the right ventricle and pulmonary artery in every instance with an average gradient of only 5 mm. Hg.

The gradient between the pulmonary artery and the right ventricle during diastole was significantly decreased in two patients in whom the pulmonary valve was widely excised. The pulmonary arterial diastolic pressure in these patients was 3 and 5 mm. Hg, respectively (fig. 8).

DISCUSSION

The clinical evaluation of these patients following surgery was not considered to be significant in a critical evaluation of the success of the operative procedure. There were four patients who were cyanotic prior to operation and each presented some degree of dyspnea and fatigue with exertion. Definite improvement in exercise tolerance was described following surgery in these patients. Relief of symptoms bore no relationship to degree of improvement of the hemodynamic pattern following surgery. No definite or significant symptomatology was described by the remaining six patients. Thus, it is not considered that the evaluation of symptomatology prior to and following operation is of any significant value in determining the extent to which the valvular pulmonic stenosis has been relieved. Definite conclusions regarding the degree of improvement following surgery

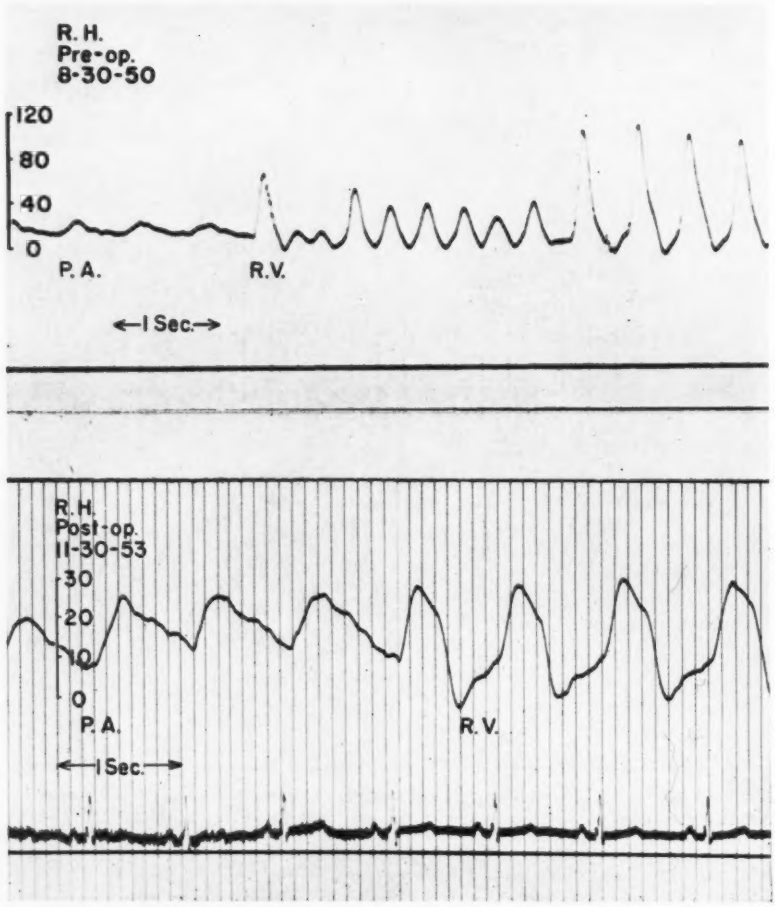

FIG. 6. Reduction of right ventricular pressure to normal and restoration of normal pulmonary arterial pressure and pulse contour following transarterial valvulotomy. The pressure gradient between the right ventricle and pulmonary artery has been abolished. (R. H. group B.)

can only be based on objective physiologic data rather than subjective impressions.

Similarly, the physical examination is not considered to offer criteria for precise evaluation of operative results; however, certain trends were noted. While the intensity of the systolic murmur tended to decrease in all patients, a more pronounced and uniform decrease was present in the patients in whom transarterial direct valvuloplasty was performed. This uniform decrease in intensity of the systolic murmur in the latter group tended to parallel the more complete obliteration of the pressure gradient between the right ventricle and the pulmonary artery as determined by right heart catheterization.

The increase in intensity of the second heart sound in the left second intercostal space following surgery is a finding that is not well understood. It has generally been considered that the diastolic pressure in the pulmonary artery is the major factor governing the relative intensity of the second heart sound in this area. Certainly the increased intensity does not reflect an increased pulmonary arterial diastolic pressure in these patients, since this pressure level was lower postoperatively than prior to surgery in all patients

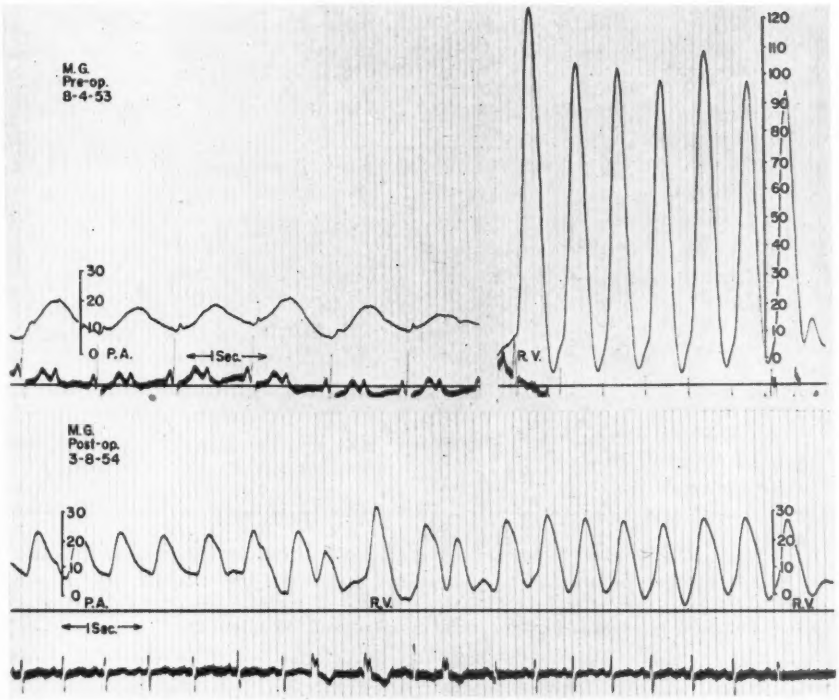

FIG. 7. Reduction of the right ventricular pressure to normal levels and return of pulmonary artery pressure and contour to normal following transarterial pulmonic valvulotomy. This tracing was recorded following exercise. (M. G. group B.)

in group B. It is postulated that the increased intensity of this sound following surgery might be due to an increased mobility of the incised pulmonic valve.

The appearance of a diastolic murmur in all patients operated by the transarterial approach, and considered to indicate organic pulmonic insufficiency, is of considerable interest. This murmur was of a different quality than that characteristically associated with functional pulmonic insufficiency. The murmur encountered in these patients was rougher in quality and lower in pitch than the classic Graham Steell murmur.

Definite regressive changes were noted in serial postoperative electrocardiograms of all patients. The decrease in R-wave amplitude reflected the decrease in right ventricular pressure; however, no quantitative relationship was apparent. It has been demonstrated that there is a poor relationship between the degree of right ventricular hypertrophy and the level of pressure within the right ventricle.[15] Therefore, a quantitative evaluation of the postoperative results cannot be determined from a study of the electrocardiographic changes. Transition of the QRS complex in precordial lead V_1 from a right ventricular hypertrophy pattern to one suggesting an incomplete right bundle-branch block represents an interesting alteration. This phenomenon may reflect a stage in the regression of a right ventricular hypertrophy pattern or may reflect the dilatation of the right ventricle with an alteration in the type of ventricular stress, as proposed by Cabrera.[16]

The roentgenographic changes consisted principally in an increase in over-all heart size and an increase in the amplitude of pulsations within the right and left main pulmonary arteries. The increase in heart size that occurred following valvuloplasty was more pronounced in the patients treated by wide excision of the pulmonic valve, and the murmur

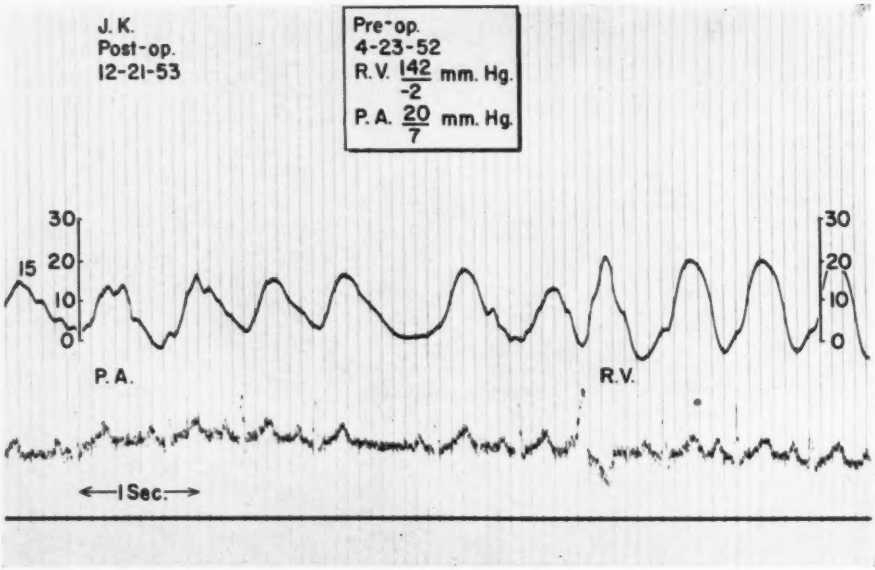

FIG. 8. Low diastolic pressure in the pulmonary artery with a low diastolic pressure gradient between the pulmonary artery and right ventricle. A pressure pattern associated with pulmonic insufficiency following transarterial pulmonic valvuloplasty. (J. K. group B.)

of pulmonic insufficiency was of greater intensity in these patients. This suggests dilatation of the right ventricle occurring as a result of an increased residual diastolic chamber volume due to the pulmonic insufficiency. An increase in heart size was also noted postoperatively in the patients not evidencing pulmonary insufficiency. In this case an increase in diastolic volume and, consequently, heart size may be a manifestation of increased stroke volume following the relief of pulmonic valve obstruction. The increase in heart size showed no progression beyond the immediate postoperative period.

There was an apparent correlation between the postoperative increase in the pulmonary artery pulse pressure and the increase in amplitude of the pulsations noted in these vessels on fluoroscopy. This relationship tends to emphasize the role of the pulmonary arterial pulse pressure in the production of pulsations in the pulmonary arteries in addition to the factor of pulmonary blood flow. Increase in pulmonary blood flow did not appear to be a factor in producing this increase in pulsations as the pulmonary artery blood flow was not significantly altered following surgery.

Pre- and postoperative hemodynamic studies form the basis for the most critical and conclusive evaluation of the efficacy of pulmonic valvular surgery. Using these criteria, the superiority of the direct transarterial valvuloplasty over the blind ventricular valvulotomy is apparent. The hemodynamic event of most significance in relief of stenosis is the obliteration of the systolic pressure gradient existing between the right ventricle and the pulmonary artery. This gradient was abolished in the patients undergoing direct valvuloplasty. The restitution of a normal pulmonary arterial pulse contour is also of importance. This dynamic change again was present uniformly in the patients treated by direct valvuloplasty. The degree of stenosis, as reflected by the level of the systolic pressure in the right ventricle was somewhat more severe in the patients in group A than in those patients in group B. However, it is not considered that this factor in any way obviates the superiority of the transarterial approach.

The significance of the creation of pulmonary insufficiency in these patients is not established at this time. To our knowledge, there is no study available of the effect of pulmonary insufficiency upon the cardiovascular system in man. The creation of pulmonary insuf-

f iency has been employed in an attempt to p oduce cardiac decompensation in the ex- p erimental animal, but it has been unsuc- c ssful.[17] The postoperative course of the p atients with pulmonic insufficiency did not c iffer in any way from the course of patients v ith no evidence of pulmonary insufficiency. S ince the pulmonary circulation is a low p ressure system and the gradient during d iastole between pulmonary artery and right v entricle is small, the creation of pulmonary insufficiency of this order should have little effect upon the dynamics of the right heart. The final answer cannot be stated at this time, and must await further evaluation. At the present time, however, it can be stated that there is no evidence of significant derangement in the hemodynamic pattern of these patients.

Summary and Conclusions

Surgical correction of isolated valvular pulmonic stenosis has been effected almost exclusively by the transventricular approach. The hemodynamic studies following this procedure reveal evidence of inadequate relief of the stenosis, and lack of uniformity of results. The advent of open heart surgery afforded by hypothermia has now permitted the direct vision of the stenotic pulmonic valve from the arterial side. This communication presents the pre- and postoperative clinical and physiologic evaluation of 10 patients with isolated valvular pulmonic stenosis. In five patients the approach to the valve was through the wall of the right ventricle, while in the remaining five patients the approach was through the pulmonary arterial wall.

Although subjective improvement was described in patients in both groups, such an evaluation of results of surgery is not considered to represent a critical analysis of the success of this operation. The physiologic studies obtained in the group in which the valve was approached through the ventricle were variable, and in no instance was there evidence of complete removal of the valvular obstruction. The physiologic data determined following the transarterial approach to the stenotic valve revealed uniformly good results. The right ventricular systolic pressure was reduced to normal levels in all five patients, and the pulmonary arterial pulse contour assumed a normal form in each instance. There was obliteration of the preoperative systolic pressure gradient from the right ventricle to the pulmonary artery in every patient. Thus, in this group complete relief of valvular obstruction was demonstrated, in contrast to the variable and inadequate relief of obstruction when the valve was approached via the right ventricle. The transarterial approach therefore, is recommended as the method of choice in the surgical therapy of isolated valvular pulmonic stenosis.

Sumario Español

La corrección quirúrgica de la estenosis pulmonar valvular aislada se ha efectuado casi exclusivamente por el aproche transventricular. Los estudios hemodinámicos que prosiguen este procedimiento revelan evidencia de una inadecuada mejoría de la estenosis y de una falta de uniformidad en los resultados. El advenimiento de la cirugía cardíaca abierta hecho posible mediante la hipotermia ha permitido la visualización directa de la válvula estenótica pulmonar desde el lado arterial. Esta comunicación presenta la evaluación clínica y fisiológica pre y postoperatoria de 10 pacientes con estenosis valvular pulmonar. En cinco pacientes el aproche a la válvula fué a través de la pared del ventrículo derecho, mientras que en los cinco restantes el aproche fué a través de la pared de la arteria pulmonar.

Aunque mejoría subjetiva fué descrita por pacientes en ambos grupos, tal evaluación de los resultados quirúrgicos no es considerada representar un análisis crítico del éxito de la operación. Los estudios fisiológicos obtenidos en el grupo en que la válvula fué aprochada a través del ventrículo fueron variables y en ningún instante hubo evidencia completa de desaparición de la obstrucción valvular. Los datos fisiológicos determinados luego del aproche transarterial a la válvula estenótica revelaron resultados buenos uniformemente. La presión sistólica ventricular derecha fué reducida a niveles normales en todos los cinco pacientes y el contorno del pulso arterial

pulmonar se tornó en normal en cada caso. Hubo obliteración de la pendiente de presión sistólica preoperatoria del ventrículo derecho a la arteria pulmonar en cada paciente. Así es que en este grupo se demostró completa desaparición de la obstrucción valvular, en contraste a la mejoría inadecuada y variable de la obstrucción cuando la válvula fué aprochada vía ventrículo derecho. El aproche transarterial se recomienda como el método preferido en la terapia quirúrgica de la estenosis pulmonar aislada.

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Antibiotic Therapy of Bacterial Endocarditis

VI. Subacute Enterococcal Endocarditis: Clinical, Pathologic and Therapeutic Consideration of 33 Cases

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Thirty-three cases of enterococcal endocarditis encountered during the decade from January 1944 through December 1953 are reviewed. In vitro studies indicate that penicillin and streptomycin are the best antibiotic pair for bactericidal effect. Twelve of the last 14 patients were cured (86 per cent), 10 with combined therapy. The cure rate in enterococcal endocarditis now approximates that of endocarditis caused by penicillin-sensitive streptococci. A maximal number of cures is achieved by individualization of therapy. The daily dosage of penicillin and the duration of combined penicillin-streptomycin therapy should be guided by in vitro bactericidal tests employing the patient's strain of enterococcus.

A DECADE ago enterococcal endocarditis was considered quite rare and only a limited number of such cases had been reported.[1-5] In 1906 Andrews and Horder[6] found *Streptococcus faecalis* to be the offending organism in 4 of 24 cases of "malignant endocarditis." In 1922 Gordon noted that 3 of 24 strains of *Streptococcus faecalis* studied came from malignant endocarditis.[7] In 1929 Dible[8] observed that in one of six cases ulcerative endocarditis was caused by an enterococcus and in 1936 Elser and Thomas[9] pointed out that *Streptococcus zymogenes* was not infrequently isolated from patients with bacterial endocarditis. Of the 17 strains studied, eight were obtained from the blood and six of these were from patients with endocarditis. Following Sherman's[10-12] definitive work concerning the differentiation of enterococci from other streptococci, Moran[13] studied 20 organisms from patients with endocarditis and found that 20 per cent of them were enterococci. In 1942 Skinner and Edwards[14] reviewed 37 cases collected from the literature and added two cases of their own. Wheeler and Foley observed that 4 of 23 patients with nongroup A streptococcal infections had enterococcal endocarditis.[15] MacNeal and Blevins found that in 6 of 36 patients bacterial endocarditis was caused by *Streptococcus faecalis*.[16]

Since the foregoing reports were made, the proportion of cases of endocarditis attributable to enterococci has been variously estimated as 3 to 8 per cent,[17] 5 to 10 per cent[18] and 10 to 15 per cent.[19] In a series of 46 patients with endocarditis treated at the Mayo Clinic from October, 1950, through May, 1952, enterococci were implicated in 10 instances, a proportion of 21 per cent.[20] This proportion approximates that found in recent publications. Today the proportion of cases of endocarditis caused by enterococci seems to be increasing.[21, 22] This apparently reflects a decreased prevalence of endocarditis caused by penicillin-sensitive streptococci of the salivary or viridans type.[21,22]

We propose in this paper to report our experiences with enterococcal endocarditis seen at the Mayo Clinic during the first decade of antibiotic therapy for bacterial endocarditis. We wish to consider particularly some of the therapeutic problems that arise in the antibiotic therapy of this valvular infection caused by penicillin-resistant streptococci.

METHODS*

From January, 1944, through December, 1953, 33 cases of enterococcal endocarditis were encountered

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* The bacteriologic procedures in this study were performed in the Section of Bacteriology under the

at the Mayo Clinic. These constitute an unselected consecutive series of cases and represent approximately 10 per cent of the total number of patients with endocarditis seen during this period. As a result of this experience, a definite plan of study and therapy of enterococcal endocarditis has evolved.

In vitro sensitivity tests are carried out by the plate dilution method. Uniform amounts of a pure culture which have been incubated for six hours are spread evenly over the surfaces of a series of blood-agar plates containing twofold dilutions of the antibiotic. The plates are incubated at 37 C. for 24 hours, and the sensitivity recorded represents the concentration of antibiotic which completely inhibits growth of the organisms. A standard strain of *Micrococcus pyogenes* having a known degree of sensitivity to the antibiotic is used as a control. Assays for serum concentrations of penicillin are carried out by the Fleming slide cell technic.[23] A tube dilution method using *Klebsiella pneumoniae* as a test organism is utilized to determine the serum levels of dihydrostreptomycin.

Tests were carried out to determine the bactericidal effect of penicillin, dihydrostreptomycin, chloramphenicol, oxytetracycline (terramycin) and erythromycin, singly and in combinations, on five of the strains of enterococci isolated (cases 21, 27, 29, 30 and 33). (Case numbers used in this paper correspond to those in tables 7 and 8.) The antibiotics were added to heart infusion broth containing approximately 4,000 actively growing organisms per milliliter. After incubation at 37 C. for 18 hours the organisms were subcultured on solid or semisolid media to determine the number of survivors. In each case penicillin and dihydrostreptomycin were found to be the most effective pair of antibiotics for bactericidal effect. Although the organisms were relatively insensitive to dihydrostreptomycin, the addition of this antibiotic to penicillin considerably increased the bactericidal effect over that of penicillin alone. Under the conditions of the test, killing of the organisms was complete with concentrations of the two antibiotics ranging from 2.5 units of penicillin and 2.5 micrograms of dihydrostreptomycin per milliliter to 5 units of penicillin and 5 micrograms of dihydrostreptomycin per milliliter. The addition of erythromycin or bacitracin to the penicillin-dihydrostreptomycin combination was not advantageous.

An attempt was made to gauge the probable effectiveness of antibiotic therapy by determining the bactericidal effect of the patient's serum against his own organism while he was under treatment.[24] Serial 1:1 dilutions of the serum were made with heart infusion broth and these together with undiluted serum were seeded with a six-hour culture of the organism to give approximately 4,000 bacteria per milliliter. After 18 hours of incubation, cultures were made from each tube to determine the number of surviving organisms. Such studies, carried out in cases 31, 32 and 33, indicated that total killing of the organism occurred in a 1:8 dilution of the serums of all three patients when they were receiving daily 20, 20 and 50 million units of penicillin respectively and 2 Gm. of dihydrostreptomycin.

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Bacteriology of Enterococci

The enterococci belong to group D of Lancefield's classification of streptococci. They are differentiated from other streptococci by the serologic reaction of precipitation with Lancefield's group D streptococcal antiserum.[11] *Streptococcus faecalis*, *Streptococcus liquefaciens*, *Streptococcus durans* and *Streptococcus zymogenes* are the four species that are classified as enterococci. For practical clinical and therapeutic purposes, the enterococci can be considered as one since they are highly resistant to penicillin. They are quite hardy, are of low virulence and grow well in ordinary laboratory media. Most enterococci are inhibited by 2 to 12 units of penicillin per milliliter.[25, 26] Rarely, strains are inhibited by 0.1 unit or less of penicillin.[27, 28] Enterococci are normally found in the human intestine and vagina, and in milk and dairy products.

The enterococci are differentiated by means of varying biochemical and physiologic characteristics but for practical purposes no attempts were made to determine the species of the strains of enterococci isolated herein; only the bacteriologic procedures necessary for the identification of the bacteria as enterococci were carried out. Of the 33 patients in this series from whom enterococci were isolated, in vitro sensitivity tests with penicillin, dihydrostreptomycin and other antibiotics were carried out on 31 (table 1).

Pathogenesis

Bacteremia occurring in the face of antecedent disease of or operation on the genitourinary or gastrointestinal tract should cause one to consider the likelihood of an enterococcal infection. Urologic manipulation, perforative lesions of the lower part of the intestinal tract and septic abortion may initiate such bactere-

TABLE 1.—*In Vitro Sensitivity of 31 Strains of Enterococci to Various Antibiotics*

	Concentration*							
	0.2	0.4	0.8	1.6	3.2	6.2	>6.2	25.0 or more
Penicillin†			1	6	15	12	4	1
Dihydrostreptomycin							2	16
Bacitracin	1	1	1	3	1			
Oxytetracycline		1	3	4	2	1		
Chlortetracycline		1	4	5	4			
Erythromycin	1	1		3	1			
Chloramphenicol						1		

* In units per milliliter of medium for penicillin and bacitracin; in micrograms per milliliter for all others.

† Total is more than 31 since in vitro sensitivity determinations made on organisms isolated during relapses are included.

TABLE 2.—*Precipitating Factors in Enterococcal Endocarditis*

Factor	Cases
Urologic procedure	16
Transurethral resection	12
Cystoscopy (for tumor or stone)	2
Nephrectomy	1
Catheterization and sounding	1
Infection	3
Pyelonephritis	2
Periapical abscess of teeth	1
Uterine factor	5
Abortion	3
Dilatation and curettage	1
Normal pregnancy	1
Hemorrhoidectomy	1
None	8
Total	33

mia. Isolated bacteremia due to enterococci occurs occasionally; repeated detection of this organism in the blood stream almost invariably signifies endocarditis.

While in the majority of cases enterococcal endocarditis is associated with organic heart disease, the infection may be engrafted on normal heart valves. This aspect of enterococcal endocarditis will be commented on later.

Enterococcal endocarditis may complicate urologic instrumentation[29, 30] such as cystoscopy, urethral dilatation or transurethral resection. This infection has been associated with or complicated carcinoma of the sigmoid colon,[28] so-called Blalock-Taussig operation,[31] abortion[32] and normal pregnancy.[33] Periapical dental abscesses have also been implicated.[34]

The precipitating factors in our cases are given in table 2.

SYMPTOMATOLOGY

Twenty of the 33 patients with enterococcal endocarditis in our series were men. The ages ranged from 25 to 77 years; the average age was 51 years. In 15 cases there was no knowledge of antecedent valvular disease. The remaining 18 patients were aware of heart murmurs.

The onset was gradual in 22 cases and acute in nine; in two cases it was not possible to describe the type of onset properly. The nine patients who had an acute onset were able to relate the first symptom precisely to a certain time. Headache, chills and fever, or embolization were, singly or in combination, the first symptoms of the disease.

Every patient had fever at some time during the course of the disease (table 3). In 11 cases the fever was low grade, that is, the temperature did not exceed 102 F. In the remaining 22 cases the temperature often ranged as high as 103 to 106 F. The higher spikes of fever usually were associated with chills.

Eleven patients had symptoms referable to the central nervous system. Five of these had hemiplegia; two of the latter became comatose and died, one recovered completely after two such episodes and two retained residua. Two patients complained of severe occipital headaches without definite evidence of cerebral embolism. One patient experienced homonymous hemianopsia and one had terminal and generalized convulsions.

Eleven patients complained of generalized arthralgias. Two others suffered from severe myalgias. One of these was referred because of "acute arthritis of the cervical spine"; no primary disease of the vertebrae was found to explain the complaint and the condition subsided with treatment of the endocarditis. The other of the two patients was distraught be-

TABLE 3.—*Symptoms in 33 Cases of Enterococcal Endocarditis*

Symptom	Cases
Fever	33
Loss of weight	23
Chills	19
Cardiovascular	17
Gastrointestinal—anorexia	16
Rheumatic—arthralgias	15
Genitourinary*	13
Sweats	12
Central nervous system	11
Respiratory	6

* In only 1 case were the genitourinary symptoms due to bacterial endocarditis.

TABLE 4.—*Physical Signs in 33 Cases of Enterococcal Endocarditis*

Sign		Cases
Heart murmur*		33
Apical systolic	19	
Aortic systolic	13	
Aortic diastolic	9	
Apical diastolic	2	
Roger type	1	
Embolic phenomena		23
Enlarged heart		18
Sinus tachycardia (above 100 per min.)		15
Splenomegaly		14
Clubbing of digits		11
Heart failure		8
Precordial thrill		8
Fundic hemorrhages		4
Hypertension		3
Auricular fibrillation		3
Hypotension		2

* Total of breakdown is more than 33 because several patients had more than one murmur.

cause of shoulder aches which also subsided with treatment of the endocarditis. Two patients had red, hot, tender, swollen ankles.

PHYSICAL FINDINGS

The most prominent physical findings were related to the cardiovascular system. Each patient exhibited a heart murmur (table 4).

It was difficult to be certain of the etiologic types of heart disease. In 11 cases there was definite evidence of pre-existing rheumatic heart disease, in five the rheumatic origin of the heart disease was questionable and in two the heart disease was congenital. The other 15 patients probably did not have underlying heart disease.

TABLE 5.—*Laboratory Data in 33 Cases of Enterococcal Endocarditis*

		Cases
Elevated sedimentation rate* (>30 mm. in 1 hr.)		32†
Anemia (<12 gm. of hemoglobin per 100 ml.)		24
Microhematuria		22
Without primary genitourinary disease	11	
With primary genitourinary disease	11	
Normal leukocyte count		20
Leukocytosis (>10,000 per cu. mm.)		12
Elevated blood urea		9
Neutrophilia (>80 per cent neutrophils)		6
Leukopenia (<5,000 cells per cu. mm.)		1

* Westergren method.

† Eight patients had sedimentation rates in excess of 100 mm. in 1 hour.

Embolic phenomena were detected in 23 patients. Five of these had pulmonary infarction. Three patients experienced clinically substantiated embolism of the eyes and these are to be distinguished from two patients who had retinal hemorrhages that were not related to obvious embolism; two of the three patients also exhibited retinal hemorrhages. Five patients had intracranial embolism with resultant paralysis. Three had splenic infarction and two of these also had suffered from ocular embolism. One patient each apparently experienced mesenteric and coronary embolism. The remaining sites of embolism were the extremities; three of the patients with emboli elsewhere also had emboli lodge in arterial channels of the extremities. Eight patients exhibited petechiae; only two of these did not suffer from major embolism. Four patients had Osler's nodes and all of these had major embolism. No patient had so-called Janeway nodes.

Laboratory data are summarized in table 5.

PATHOLOGY*

Although the clinical picture and course of enterococcal endocarditis are similar to those

* We are indebted to Dr. Jesse E. Edwards, Section of Pathologic Anatomy, for review of the pathologic material in this series of cases.

TABLE 6.—*Enterococcal Endocarditis: Cardiac Findings at Necropsy in 6 Cases*

Case	Age, Sex	Duration of Disease	Cardiac History*	Cause of Death	Necropsy Data	Comment
2	48 M	>2 mo.	No hist. of RF, HD or M	Cerebral embolism, infarct	Vegetations on normal mitral valve	See Comment, table 7
12	63 M	5 wk.	No hist. of RF, HD or M	Renal insuf.	Vegetations on normal mitral valve	See Comment, table 7. Also given 2–4.5 Gm. of chlortetracycline for 13 da. without benefit. Total period of therapy: 40 da.
13	77 M	9 da.	No hist. of RF, HD or M	Progressive deterioration	Vegetations on normal mitral valve	See Comment, table 7. SBE suspected 1 da. before death
14	53 F	>7 mo.	Min. apical sys. M appeared 6 mo. after onset of dis. No prev. hist. of RF, HD or M	Progressive heart failure	Many large vegetations on normal tricuspid valve. Lesser vegetations on mitral & aortic valves	See Comment, table 7. Intermittent antibiotic therapy at home for recurrent "episodes of pulmonary disease"
24	65 M	3 yr.	M noted 18 mo. after onset of dis. No prev. hist. of RF, HD or M	Cerebral embolus, infarct	Vegetations on bicuspid aortic valve	See Comment, table 8. Rectal cancer & a pararectal abscess also present
31	38 F	20 mo.	No hist. of RF, HD or M	Cerebral embolus, infarct	Vegetations on normal mitral valve	See Comment, table 8

* See table 7 for abbreviations.

seen in other types of nonhemolytic streptococcal endocarditis, it has been stated that enterococcal valvular infections are associated at necropsy with an increased incidence of suppurative lesions in peripheral organs and in the heart, a very low incidence of focal and diffuse glomerulonephritis, and evidence of more frequent occurrence in persons who previously had normal hearts and normal valves.[35] With this in mind, we reviewed the clinical and postmortem data in the six cases in which necrospy was performed in this series (table 6).

These postmortem studies indicate that in five of the six cases there did not appear to be any definite evidence of pre-existing valvular disease. In each of the five, however, there were minor thickenings of the chordae tendineae and valves which were attributed to bacterial endocarditis. In cases of bacterial endocarditis in which evidence of previous valvular disease is minimal, it often cannot be stated with any certainty that any in fact existed. Some of the minimal thickening in the five cases just mentioned might conceivably have resulted from pre-existing rheumatic inflammation but if this is so then the thickening had no characteristic rheumatic features such as fusion between leaflets or shortening of the chordae.

In five cases abscess formation was absent; abscesses were noted in the lungs in case 14 (table 6) in which the endocarditis arose from the tricuspid valve. The kidneys were involved in all six cases; the findings consisted of tubular hemorrhage (three cases), gross infarctions (three cases), acute diffuse glomerulonephritis (one case), foci of fibrinoid necrosis of glomerular tuft (one case) and thickening of the basement membrane (one case).

Therapy of Enterococcal Endocarditis

The treatment of penicillin-resistant enterococcal endocarditis was very unsatisfactory prior to the introduction of combined penicillin-streptomycin therapy.[36] Endocarditis caused by penicillin-sensitive streptococci had responded readily to penicillin therapy, but enterococcal endocarditis had failed to respond in most instances when penicillin was used alone. Only in the last half-decade have the results of combined antibiotic therapy for this form of endocarditis approached those of the form caused by penicillin-sensitive organisms. A spontaneous cure of the infection of bacterial endocarditis occurs occasionally.[37] Whether enterococcal endocarditis ever heals spontaneously is not known but probably it does rarely.[19, 38]

Penicillin

A number of cases have been reported in which penicillin alone or penicillin together with caronamide or probenecid (Benemid) has resulted in cure of enterococcal endocarditis. Harris[39] in 1945 cited a cure in which 24 million units of penicillin alone over a 76-day period resulted in eradication of the infection.

In 1946, MacNeal and colleagues[19] reported a case in which a clinical arrest of enterococcal endocarditis followed long-term therapy with a combination of enterococcal bacteriophage and penicillin. The organism in this case was very resistant to penicillin but quite sensitive to bacteriophage. Subsequent to these two communications, additional reports of cures of enterococcal endocarditis with penicillin alone or together with renal tubular blocking agents [27, 28, 33, 40-44] have appeared. In these cases, total doses of penicillin varying from 12.5 to 1,852 million units and given for periods ranging from 28 to 66 days proved successful. Very high blood levels of pencillin, ranging up to 100 units or more per milliliter of medium, were obtained often in these cases.

As has been previously noted, almost all enterococci are resistant to the action of penicillin.[18, 25, 26] Mathews[27] and McCoy and Mason[28] have reported two cases of enterococcal endocarditis in which enterococci unusually sensitive to penicillin were isolated. In a recent report Baker and Pilkington[44] cited a case of enterococcal endocarditis in which the infection was not controlled by what appeared to be adequate combined penicillin-streptomycin or chlortetracycline (Aureomycin) therapy but was controlled by large daily doses of penicillin (32 million units) and probenecid (4 Gm.) for a 59-day period.

Streptomycin

The role of streptomycin in the therapy of bacterial endocarditis has been reviewed by Hunter[45] and by Wallach and Pomerantz.[46] Streptomycin used alone was found to be of little value except occasionally against a streptomycin-sensitive organism. The results of therapy of enterococcal endocarditis with this antibiotic were uniformly poor. In four cases of such infection reported by Hunter[45] streptomycin, used alone, failed. Cure was obtained in one of these cases with combined penicillin-streptomycin therapy.

Additional reports on the value of this drug in enterococcal endocarditis have appeared.[33, 47-52] In one of four cases reported by Sirota and colleagues,[49] streptomycin gave only a temporary remission. Apparently, only two of the patients included in these reports were cured with streptomycin alone.[50, 51] In two other cases failure with streptomycin was followed by cure with penicillin and caronamide.[33, 52]

The value of streptomycin in enterococcal endocarditis lies in its supportive role to penicillin. In vitro and in vivo studies[18, 53, 54] indicate that streptomycin synergizes the bactericidal action of penicillin so that endocarditis caused by penicillin-resistant enterococci is controlled in almost all cases. Further comments regarding the combined use of these two antibiotics will be made below.

Broad-Spectrum Antibiotics

Chlortetracycline. The value of chlortetracycline in the therapy of bacterial endocarditis has been reviewed recently by Friedberg[55] and by Kane and Finn[56] In 2 of the 11 cases presented by Friedberg the isolated organism was an enterococcus. Chlortetracycline alone in adequate doses for an appropriate period did not control the enterococcal infection. In ad-

ditional reports,[31, 57-63] most of the therapeutic results were said to be unfavorable even though only small amounts of the drug were required to inhibit the organism in vitro. Cures of one or two patients with enterococcal endocarditis have, however, been recorded by Long and co-workers,[58] by Harvey and co-workers[31] and by Roberts and Goldberg.[60] The case reported by Glasser and Smith[59] illustrates the usual response obtained with the drug. In three of the cases of enterococcal endocarditis reported by Finn and Kane,[56, 62] this drug was of no value in controlling the infection.

Oxytetracycline. Few reports on the value of oxytetracycline in enterococcal endocarditis have appeared.[63-66] Since this antibiotic and chlortetracycline parallel each other closely with regard to chemical structure, pharmacologic properties, bacteriostatic end points and actual therapy of patients, it would be supposed that their effects in endocarditis caused by enterococci would be similar. In the few cases in which oxytetracycline has been tried, the infection was arrested in only one instance.[64] Oxytetracycline combined with dihydrostreptomycin was unsuccessful in two cases reported by one of us.[65]

Chloramphenicol. The use of chloramphenicol in enterococcal endocarditis is mentioned briefly in several communications.[55, 56, 62, 63, 67] In most instances the drug was used in combination with other antibiotics. There have been no reports of success in the arrest of enterococcal endocarditis with this antibiotic alone. It seems to be of little or no value in this infection.

Erythromycin and Carbomycin

It was hoped that two recently introduced antibiotics with a penicillin-like spectrum, erythromycin and carbomycin,[68-72] would prove useful in the therapy of bacterial endocarditis. To date, only a few reports on this point have appeared.[70, 72-75]

The status of erythromycin in the therapy of endocarditis has been presented in another publication.[73] One of these patients had relapsing enterococcal endocarditis. Erythromycin in doses of 0.5 Gm. was given every six hours for a month. Symptomatic improvement occurred but the blood cultures never became negative. The drug merely suppressed growth of the organisms so that cultures became positive only after periods as long as 15 days. In vitro studies of these organisms did not reveal any synergistic bactericidal effects when erythromycin and penicillin were used together.

Carbomycin in adequate dosage was found to be ineffective in two cases of enterococcal endocarditis.[72] Since erythromycin and carbomycin tend to behave like bacteriostatic antibiotics both in vitro and in the treatment of endocarditis[76, 77] and since most enterococci are relatively insensitive to them, it is unlikely that these drugs either alone or in combination with other antibiotics will prove to be of much value in enterococcal endocarditis.

Penicillin-Streptomycin Combination

Since Hunter's[45] first communication concerning the cure of a patient of enterococcal endocarditis with a combination of penicillin and streptomycin, an increasing number of reports have attested to the value of this antibiotic combination for penicillin-resistant streptococcal valvular infections.[17, 18, 78, 79] These reports on patients actually treated confirmed the in vitro studies of Hunter[53], Jawetz and Gunnison[54] and Spicer.[80] These workers had demonstrated that penicillin and streptomycin had a definite synergistic bactericidal action on the enterococcus when they were used together in the test tube. The results of in vitro studies have enabled the clinician to obtain as high a percentage of cures in cases of penicillin-resistant enterococcal endocarditis as has been obtained in cases of penicillin-sensitive endocarditis. Robbins and Tompsett[18] were able to control the valvular infection in seven of nine patients to whom adequate combined therapy had been given. Hunter in more recent communications[22, 78] has said that 10 million units of pencillin and 2 Gm. of streptomycin should be given daily for six weeks in order to achieve a maximum of cures.

To date, only the antibiotic combinations of penicillin-streptomycin and penicillin-bacitracin[81] have been successful in controlling enterococcal endocarditis. The antibiotic

combinations of oxytetracycline-dihydrostreptomycin,[65] chlortetracycline-streptomycin,[79] penicillin-chlortetracycline,[62] chlortetracycline-chloramphenicol,[63] and penicillin-chloramphenicol[62] have failed.

Therapy in Present Series of Cases

The significant clinical features and the data concerning the treatment of the patients reported herein are given in tables 7 and 8. In table 7 are listed the patients who were treated with penicillin. Most of the 11 patients treated unsuccessfully were seen during the first half-decade (1944 to 1948 inclusive) of antibiotic therapy for bacterial endocarditis, when the efficacy of penicillin for this purpose was being determined. The daily doses ranged from 0.1 to 15 million units and the duration of treatment was from 10 to 126 days. These patients received what would now be considered inadequate therapy. Several, however, were treated with fairly large daily doses of penicillin and for long periods without success. In the seven cases in which treatment was successful the daily doses of penicillin ranged from 2 to 12 million units, and the duration of therapy ranged from 17 to 63 days.

A study of the data in this series leads to the conclusion that there is little correlation between the in vitro sensitivity of the isolated organisms and the effectiveness of therapy given. The results of the in vitro sensitivity tests were roughly similar in the two series. Unfortunately, bactericidal end points were determined in only one instance.

Of the 33 patients in this series, 31 received antibiotic therapy; in the others, the diagnosis was made only at postmortem examination. One patient (case 10) had marked hypersensitivity to penicillin and hence could not be treated with this drug. Dihydrostreptomycin alone was given in doses beginning with 0.25 Gm. and gradually increasing to 4 Gm. per day. Therapy was given for three weeks; the patient became afebrile and the sedimentation rate dropped from 67 to 12 mm. Nevertheless, the patient deteriorated progressively and finally died. In all, 16 of the 33 patients (48 per cent) died. However, only two of the last 14 patients (14 per cent) given appropriate combined therapy (12 patients) or penicillin alone (two patients) succumbed to their disease; these two deaths were from cerebral embolism and massive cerebral infarction.

Seven of 31 patients given antibiotic therapy were cured with penicillin alone (22 per cent). Eleven of 18 patients treated with penicillin alone represented failures (61 per cent) (table 7).

Table 8 presents the pertinent data on the 14 patients given combined penicillin-dihydrostreptomycin therapy. Control of the infection was achieved in 12 of the 14 patients given adequate antibiotic therapy (86 per cent); in 10 patients this was achieved with combined therapy, and in the two others with penicillin alone. Two patients died of massive cerebral hemorrhage and cerebral embolism respectively 9 and 17 days after antibiotic therapy was begun.

Ten of the 12 cured patients were given combined therapy, 6 million to 50 million units of aqueous crystalline penicillin per day by continuous intravenous drip for 4 to 10 weeks, and dihydrostreptomycin sulfate, 1 to 2 Gm. per day, was given for a similar period. In another patient (case 21), combined penicillin-dihydrostreptomycin therapy was given for 10 days and then penicillin alone (7 million units per day) was given for 60 more days. In the latter instance, bactericidal tests indicated antagonism between penicillin and dihydrostreptomycin with a grown-out seven-hour culture and a lack of additive or synergistic bactericidal effect with an actively growing two-hour culture under the conditions of the tests. The patient who was given combined therapy for only three weeks (case 20) had a relapse shortly after arriving home. Cure was achieved with 12 million units of pencillin a day for a period of eight weeks (table 7).

Relapses occurred in 5 of the 12 living patients; all five were retreated successfully (table 8). Four of the five patients were given what now is considered inadequate therapy. In the fifth patient, adequate dosage of the combined antibiotics for five and one half weeks was ineffective. One patient (case 20) was treated for only three weeks, since he insisted on going home. The infection was of one

TABLE 7.—*Enterococcal Endocarditis Treated With Penicillin Alone*

Case	Age, Sex	Type of Heart Disease*	Penicillin Sensitivity†	Penicillin Therapy‡			Comment
				Daily dose	Days treated	Total dose	
			Treatment failures				
1§	52 M	RHD; apical sys. M	—	.1–.2	31	4.1	No response to therapy. Death from infection
2§	48 M	Apical sys. M‖	1.6	.16–4.0	45	130	No response to therapy with increasing doses of Pen. Organism inhibited by 0.8 unit Pen. at onset of therapy
3§	68 M	RHD?; aortic sys. M	1.6	8.0	21	168	Good response to therapy. Temperature normal in 2 da. Afebrile 24 da. before dismissal. No follow-up. Cure?
4§	62 M	Aortic sys. & dias. M‖	10.0	0.08–0.1	20	2.0	TUR complicated by staph. bacteremia. Latter cured with Pen. SBE noted 2.5 mo. later; no M at time of staph. bacteremia. Death from uncontrolled infection
5§	73 M	Apical sys. M‖	>25.0	0.3–5.4	10	27.5	Death from infection
6	55 M	Apical sys. M‖	1.6–6.0	6.0–10.0	126	1,133	Four episodes of therapy; last episode: 10 million units daily for 8 wk. Good clinical response & neg. blood cultures with each course but relapse each time. Death from infection
7§	63 M	RHD; aortic sys. M	3.2	0.3–4.0	11	29	No response to therapy. Death 3 wk. after TUR
8	25 F	RHD; apical sys. M	1.6	5–20	49	595	Bacteremia & fever continued with increasing daily Pen. dosage. No response to therapy. Organism increasingly resistant to Pen. Death from uncontrolled infection
9	27 F	RHD; aortic dias. & apical sys. M	>3.2	15	56	840	Therapy by home physician. Relapse 1 mo. after treatment discontinued. Death from infection
10	57 M	RHD; sys. & dias. aortic M	3.2	—	—	—	Patient very sensitive to Pen. 5,000 units 2 times at clinic caused hemorrhagic rash of legs. 12,000 units at home caused generalized desquamating rash. Treatment with streptomycin alone. Death from uncontrolled infection
11	62 M	Aortic dias. M‖	3.2	6	21	126	Good response to therapy. Sed. rate dropped from 112 to 52 mm. Congestive failure at home. Rehospitalized 11 days: no fever, and neg. blood cultures. Death from heart failure. Pen. cure?

TABLE 7.—(*Continued*)

Case	Age, Sex	Type of Heart Disease*	Penicillin Sensitivity†	Penicillin Therapy‡			Comment
				Daily dose	Days treated	Total dose	
12	63 M	Apical sys. M‖	1.6	1.2–7	40	120	Mixed infection: SBE with A. aerogenes also (8 pos. cultures); organism resistant to then known antibiotics. Death from renal insufficiency. No response to therapy
13	77 M	Apical sys. & dias. M‖	—	—	—	—	No therapy. Death 9 da. P.O. Organism isolated at necropsy
14	53 F	Apical sys. M‖	10.0	—	—	—	No therapy. Death from heart failure <48 hr. after admission
			Treatment cures				
15	40 F	RHD; apical sys. M	>10.0	2±	63	90	40,000 units given orally every 3 hr. for 1 mo. with failure. Then IM and IV Pen. for 9 wk. with cure. Follow-up: 8 yr.
16¶	25 F	CHD; VSD Roger type M	3.2 6.2	10 5–10	22 15	227 100.4 327.4	Relapse 3 wk. after first course of therapy. Second course stopped after 15 da. because of multiple abscesses in buttocks. Nine subsequent blood cultures neg. Follow-up: 6 yr.
17	63 M	Apical sys. M‖	3.2	3–10	34	213	Therapy uneventful. Continued with 50,000 units orally 6 to 8 times a day for 1 mo. at home. Follow-up: 5 yr.
18§	68 M	RHD?; Apical sys. M	3.2	10	17	170	Good response. Nine subsequent cultures neg. Follow-up: 5 yr.
19	67 M	Apical sys. M‖	3.2	1.2–4.8	25	76.6	No M on admission. Two wk. later soft apical sys. M becoming louder. Death after pneumonectomy for bronchogenic cancer 9 mo. later. Heart neg. at clinic in 1937 and 1945
20	75 M	HHD & RHD; aortic sys. M	>3.2	12	56	672	Dihydrostreptomycin given with first course (See table 8). Second course by home doctor. Follow-up: 1 yr.
21	33 F	Apical sys. M‖	0.8	7.2	70	540	See table 8. 1 Gm. dihydrostreptomycin given first 10 da., then discontinued. Follow-up: 3 yr.

* Abbreviations: CHD = congenital heart disease; HD = heart disease; HHD = hypertensive heart disease; IM = intramuscular; IV = intravenous; M = heart murmur; RF = rheumatic fever; RHD = rheumatic heart disease; SBE = subacute bacterial endocarditis; sys. and dias. = systolic and diastolic; TUR = transurethral prostatic resection; VSD = ventricular septal defect.

† Penicillin in units per milliliter of medium.

‡ Dosage in millions of units.

§ Reported previously by Merritt.[39]

‖ No history of rheumatic fever, heart disease or heart murmur before treatment at Mayo Clinic.

¶ Reported previously by Hagedorn and Scheifley.[41]

TABLE 8.—*Enterococcal Endocarditis Treated With a Combination of Penicillin and Dihydrostreptomycin*

Case	Age, Sex	Type of Heart Disease*	Penicillin Sensitivity†	Penicillin Therapy‡			Dihydrostreptomycin Therapy¶			Follow-Up	Comment
				Daily dose	Days treated	Total dose	Daily dose	Days treated	Total dose		
22	75 M	HHD & RHD; aortic sys. & dias. M‖	>3.2	0.6–6 12.0	22 56	66.5 672 738.5	1–2	22	34.5	1 mo. 2 yr.	Failure with 3 wk. combined therapy. Further treatment refused after 3 wk. Relapse at home 1 mo. later. *Cure* with Pen. alone
	33 F	Apical sys. Aur. fib. M‖§	3.2 0.8	6.0 7.2	28 70	143 504 647	1	10	10	4 mo. 3 yr.	Combined treatment changed to Pen. Well for 4 mo. after 1st course Pen.; then reinfection? Second course: no response to oxytetracycline-DHS for 1 wk.; Pen.-DHS given only 10 da.; bactericidal tests showed Pen. more effective alone; blood Pen. levels ranged from 2–32 units (average 11) throughout treatment; probenecid given. *Cure* with Pen. alone
	48 F	RHD. Aur. fib. Aortic & apical sys. & dias. M	3.2	10	42	420	1–2	42	56	>1 yr.	*Cure*. Probenecid caused severe heartburn, nausea, abdominal pain. Treated for cong. heart failure 6 mo. before therapy. Pen. blood levels averaged 16 units throughout treatment
23	23 F	Apical sys. M§	3.2	10	35	350	1–2	35	63	>1 yr.	*Cure*. High febrile reaction in last 2 wk. of treatment (104 F.) due to polythene needle. Pen. blood levels averaged 16 units
24	65 M	CHD. Bicuspid aortic valve. Aortic sys. M	3.2	10	9	90	2	6.5	13	—	*Death* on 9th day of treatment due to massive cerebral hemorrhage from cerebral embolus to rt. midcerebral A. Endocarditis present >3 yr. Blood cultures became neg. after treatment started
25	54 F	RHD? Aortic sys. M	>3.2	10	38	380	1–2	38	52	2 yr.	*Cure*. Uncomplicated recovery
26	58 M	RHD? Apical sys. M	1.6	6.0	28	168	1–2	32	42	2 yr.	*Cure*. Uneventful recovery
27	35 F	Aortic Sys. & dias. M§	3.2	15	41	615	1–2	27	39	2½ yr.	*Cure*. Uneventful recovery. Home doctor could detect no M before admission here
28	25 F	Apical sys. M§	>3.2	10	28	280	1–2	28	38	2 yr.	*Cure*. Uneventful recovery with 1 mo. of therapy—organism resistant to >3.2 units of Pen.
29	62 M	RHD? Aortic sys. M‖	3.2 3.2	5–8 15	28 42	156 630 786	1 1–2	28 35	28 42 70	1½ yr. 3 yr.	*Cure*. Failure with oxytetracycline-DHS initially and with 1st course of Pen.-DHS for 4 wk.; uneventful cure with 2nd course
30	50 M	RHD. Aortic sys. & dias. M‖	1.6 3.2 6.2	10 15 30	38 50 70	380 750 2,100 3,230	1–2 1–2 2	38 50 70	65 89 140 294	3 mo. 2 mo. 18 mo.	*Cure*. Relapsing enterococcal endocarditis. Pen.-DHS therapy failed on 2 occasions. 1 mo. of erythromycin also failed (see text). Probenecid given with last 2 courses
31	38 F	Apical sys. M§	5.0	10–20	17	200	2	17	34	—	*Death* on 17th day of therapy as result of cerebral embolism. Temp. fell to normal day after treatment started. Subsequent cultures neg. Probenecid not tolerated
32	68 M	RHD. Aortic sys. M	5.0	10–20	42	580	1–2	42	81	1 yr.	*Cure*. Uneventful recovery. Pen. increased from 10 to 20 million units when bactericidal tests indicated little killing with smaller Pen. dose & DHS. Probenecid given
33	30 F	RHD with aortic sys. & dias. M‖	5.0 10.0	10 15–50	28 70	280 2,780 3,060	1–2 2	28 63	55 126 181	1 mo. 6 mo.	*Cure*. Organism not killed by 100 units of Pen. or 100 mg. of DHS. 50 million units of Pen. given by IV drip for last 40 da. Probenecid not used—caused severe epigastric burning, nausea, anorexia

‡ See table 7 for definitions.
§ No history of rheumatic fever, heart disease or heart murmur before treatment at Mayo Clinic.
* Dosage in grams.
‖ Relapse after first course of therapy.

week's duration, and the patient was afebrile and the cultures were free of growth very soon after the institution of therapy. Still, relapse occurred within a month; cure was achieved with 12 million units of penicillin daily for eight weeks.

In one case (case 21) the first course of therapy was with penicillin alone. The patient did well for four months. After symptoms recurred, the in vitro sensitivity of the isolated organism was two dilutions less than that of the organism obtained initially. It would seem that the cure of this apparent reinfection was achieved by penicillin alone, since during the second course of therapy only 1 Gm. of streptomycin a day was given for 10 days together with penicillin. In the remaining three patients who had relapses, penicillin in doses of 10 to 50 million units and streptomycin in doses of 1 to 2 Gm. per day for a period of 6 to 10 weeks were needed to effect cures of these infections. Probenecid was apparently helpful in one of these five patients (case 30).

Case Reports

Pertinent problems in the antibiotic management of enterococcal endocarditis are illustrated by the following four cases.

Case 30. A 50 year old man was first admitted with a four-month history of low-grade fever (temperature up to 101 F.), occipital headaches, arthralgias, malaise, weakness, intermittent episodes of neck pain which extended into the right shoulder, and a 30-pound loss of weight. The onset had been sudden with headache, chill and rise in the temperature to 104 F. The positive findings were: rheumatic heart disease with an enlarged heart and aortic and mitral valvular involvement, the predominant lesion being aortic insufficiency; clubbing of the fingers; Osler's nodes; mild anemia; sedimentation rate of 108 mm. in one hour; minimal microhematuria; and three blood cultures positive for enterococci. In vitro sensitivity tests revealed the bacteriostatic end point to be 1.6 units of penicillin and more than 25 micrograms of dihydrostreptomycin. The patient was given 10 million units of aqueous crystalline penicillin daily by continuous intravenous drip and 2 Gm. of dihydrostreptomycin per day divided into two doses. Therapy was continued for 38 days. Total doses of 380 million units of penicillin and 65 Gm. of dihydrostreptomycin were given, and average levels of 8 units of penicillin per milliliter of blood were obtained.

Relapse occurred in three months. At this time the patient was asymptomatic; the routine blood cultures were negative after two days of incubation and the organisms grew out in brain broth only after 15 days of incubation. The patient had been afebrile on admission and remained so through the additional 50 days of the second course of therapy. In vitro sensitivity tests disclosed a bacteriostatic end point at a concentration of 3.2 unit of penicillin per milliliter of medium. Treatment consisted of giving 15 million units of penicillin per day by continuous intravenous drip for 50 days, 2 Gm. of dihydrostreptomycin per day for 39 days and 1 Gm. per day for 11 days, and 2 Gm. of probenecid per day for 40 days and 4 Gm. per day for 10 days. Total doses were 750 million units of penicillin, 89 Gm. of dihydrostreptomycin and 120 Gm. of probenecid. An average concentration of 16 units of penicillin per milliliter of blood was obtained. Ten blood cultures during and after therapy were negative.

The patient relapsed one and one half months after completion of the second course of therapy. The third course was with erythromycin as reported elsewhere.[73] Symptomatic response occurred within a month but this new antibiotic served only to suppress the organisms. The blood cultures remained positive but required 12 to 15 days of incubation for the organisms to become evident.

The fourth course of treatment consisted of 30 million units of penicillin per day by continuous intravenous drip, 2 Gm. of dihydrostreptomycin per day (1 Gm. every 12 hours), and 2 Gm. of probenecid per day in divided doses, all for a 70-day period. The patient was dismissed and was advised to take 2 million units of procaine penicillin and 0.5 Gm. of dihydrostreptomycin every 12 hours for an additional 30 days. Hence, total doses of 2,160 million units of penicillin, 170 Gm. of dihydrostreptomycin and 140 Gm. of probenecid were given for this fourth course. For the last eight weeks of the hospital course of therapy, the blood concentration of penicillin ranged from 32 to 128 units per milliliter and averaged 64 units almost constantly. This was 10 times the in vitro sensitivity value (6.2 units per milliliter) which had been determined before the fourth course of treatment was started. Repeated cultures during therapy were negative. The period of therapy was marred only by five brief febrile episodes resulting from phlebitis caused by the plastic needle (temperature going as high as 102 F.). Audiometric and caloric tests at the close of the 70-day course of therapy gave normal results. On the twenty-ninth day of the follow-up maintenance therapy, the patient experienced slight positional vertigo. Re-examination indicated that hearing was normal; a very slight impairment of the caloric responses was noted. The subjective and objective evidence of the dihydrostreptomycin toxicity disappeared after several weeks. When last seen the patient had been completely well for 18 months without change in heart size or auscultatory findings.

The total doses for the four courses of therapy were: penicillin 3,290 million units, dihydrostreptomycin 3.4 Gm., probenecid 332 Gm. and erythromycin 6.0 Gm.

The enterococcus from this patient was subjected to extensive in vitro studies in which more than 60 bactericidal tests with seven different antibiotics were carried out with combinations of two and three of these agents. The best combination that was relatively nontoxic on systemic administration was that of penicillin and dihydrostreptomycin, 2.5 units of penicillin plus 2.5 micrograms of dihydrostreptomycin per milliliter being totally bactericidal. Other active in vitro combinations giving a total bactericidal effect were:. 2.5 micrograms of dihydrostreptomycin plus 0.312 unit of bacitracin per milliliter; 2.5 micrograms of neomycin plus 0.156 unit of bacitracin per milliliter; 1 microgram of oxytetracycline plus 1 microgram of dihydrostreptomycin plus 0.078 unit of bacitracin per milliliter; and 1 unit of penicillin plus 1 microgram of neomycin plus 0.312 microgram of oxytetracycline per milliliter.

The concentration of antibiotics required for complete killing were as follows*: penicillin and bacitracin, more than 10 units per milliliter; and streptomycin, erythromycin, oxytetracycline, neomycin and chloramphenicol, each more than 10 micrograms per milliliter.

Following our preliminary experiences with combined therapy, particularly in this case, we decided to gauge the effectiveness of our therapy in future cases with in vitro bactericidal tests employing the patient's serum against his organisms. Our last three patients were handled in this way. In each instance, the in vitro studies performed during treatment with 10 to 15 million units of penicillin by continuous intravenous drip and 2 Gm. of dihydrostreptomycin per day led to a more effective regimen of therapy and two of these three patients were cured. The other patient died, after 20 months of active valvular disease and on the seventeenth day of therapy, from cerebral embolism and massive cerebral infarction. Resumes of these cases follow.

Case 31. A woman, 38 years of age, was admitted with a 20-month history of active enterococcal endocarditis. She had had two months of combined therapy with penicillin and oxytetracycline without cure. Her symptoms consisted of intermittent chills and a temperature ranging up to 104 F., weakness, anorexia, and a 40-pound loss of weight. Sixteen months prior to admission, she had had a cerebrovascular lesion with hemiplegia. This cleared up for the most part. Nine months before admission she had had a mycotic aneurysm in the right forearm which had been excised. Findings consisted of a loud apical systolic murmur, clubbing of the fingers, splenomegaly, moderate anemia, phagocytic reticuloendothelial cells in the blood smear, elevation of the sedimentation rate, and blood cultures that were positive for enterococci. Initial in vitro sensitivity tests revealed that the organisms were inhibited by 5 to 10 units of penicillin and 0.39 microgram of oxytetracycline per milliliter. The patient was given 10 million units of aqueous crystalline penicillin by continuous intravenous drip and 2 Gm. of dihydrostreptomycin per day. Bioassays of the blood for penicillin and dihydrostreptomycin revealed values of 8 units and 64 micrograms per milliliter respectively. In vitro bactericidal tests performed with the patient's serum and organisms disclosed total bactericidal effect only in the undiluted serum and inhibition in a dilution of 1:2. Although the patient was afebrile and the cultures were free of growth, it was felt that the penicillin dosage was inadequate and hence this was increased to 20 million units per day. Bactericidal tests repeated on this altered combined regimen showed inhibition of growth at a dilution of 1:16 and a total bactericidal effect at a dilution of 1:8. With this degree of killing effect on the patient's organisms, it was felt that the antibiotic program was adequate and it was hoped that cure would be achieved eventually. However, three days after this altered program was begun the patient died from cerebral embolism and massive cerebral infarction.

Case 32. A 68 year old man gave a two-year history of gradually failing health, low-grade fever (temperature up to 101 F.), night sweats, anorexia, loss of weight, and intermittent dysuria and hematuria. The findings consisted of a moderate aortic systolic and a minimal aortic diastolic murmur, clubbing of the fingers, splenomegaly, elevation of the sedimentation rate, and enterococci in the blood cultures. In vitro sensitivity tests indicated that 5 units of penicillin, 1.5 micrograms of oxytetracycline and 1.6 micrograms of erythromycin per milliliter inhibited the organisms. The patient was started on treatment with 10 million units of aqueous crystalline penicillin-G by intravenous drip and 2 Gm. of dihydrostreptomycin per day. This was given for 21 days. Bioassays of the blood for penicillin and dihydrostreptomycin gave levels of 8 units and 16 micrograms respectively. The dose of penicillin was increased to 15 million units. The antibiotic assays remained the same on the new regimen, and this dose was given for 10 days before a change to 20 million units of penicillin per day was made. Bactericidal tests with the patient's serum while he was getting this last dosage of penicillin revealed

* Other combinations of antibiotics with erythromycin and giving total bactericidal effect are reported elsewhere.[73]

bacteriostasis in a dilution of 1:16 and total bactericidal effect in a dilution of 1:8. The dihydrostreptomycin had been replaced by a combination of dihydrostreptomycin and streptomycin and these had been continued in doses of 2 Gm. per day. Twenty million units of penicillin per day was given for 11 more days, and the total duration of therapy was 6 weeks. Probenecid in a daily dose of 2 Gm. was given for the last four weeks of treatment. Total doses of 580 million units of penicillin, 81 Gm. of streptomycin-dihydrostreptomycin and 56 Gm. of probenecid were given. No eighth-nerve toxicity was detected. Follow-up at the end of one year indicated that the patient was well.

Case 33. A 30 year old woman was admitted with a three-month history of joint pains, chills and fever, the temperature going as high as 104 F. One week before the sudden onset of chills and fever, she had had a hemorrhoidectomy. The positive findings were as follows: rheumatic heart disease with cardiac enlargement, aortic stenosis and insufficiency; mild anemia; leukocytosis; elevated sedimentation rate; and four blood cultures positive for enterococci. In vitro sensitivity tests revealed inhibition of the organism by 5 units of penicillin, 1.6 micrograms of erythromycin, and more than 50 micrograms of dihydrostreptomycin.

The patient was given 10 million units of aqueous crystalline penicillin-G by continuous intravenous drip and 2 Gm. of dihydrostreptomycin divided into two doses per day. The temperature fell to normal within 48 hours and remained so until the third week of therapy when the temperature spiked to 104 F. Recurrent spikes to 104 F. occurred daily for six days during therapy. The administration of penicillin was discontinued and the temperature was normal in 48 hours. Total doses of 280 million units of penicillin and 56 Gm. of dihydrostreptomycin were given over a 28-day period. Bactericidal tests with the patient's own serum drawn one hour before and one hour after the 1 Gm. dose of dihydrostreptomycin and employed against the patient's organism gave a total bactericidal effect only in the undiluted serum.

The patient remained well for one month when chills, temperatures up to 103 F., and positive blood cultures recurred. The temperature, however, was normal on admission and remained normal throughout the period of treatment. In vitro sensitivity tests revealed no change from the previous findings. Treatment with 15 million units of penicillin by continuous intravenous drip and 2 Gm. of dihydrostreptomycin was started and continued for 10 days when the dose of penicillin was increased to 30 million units per day. This dose was given for three weeks. Finally, the penicillin was increased to 50 million units per day. The dihydrostreptomycin was replaced by combined streptomycin-dihydrostreptomycin in the same dosage during the first week and this treatment was given for an eight-week period. Total dosages of 2,780 million units of penicillin and 126 Gm. of combined streptomycin-dihydrostreptomycin were given over the 10-week period of treatment. Probenecid could not be tolerated by the patient; the drug caused severe epigastric distress and heartburn, loss of appetite, and nausea and vomiting. The patient had remained well when last heard from six months later.

Therapy in this case was guided by numerous in vitro bactericidal tests in which the patient's serum containing the antibiotics was employed against the patient's organism. Although in vitro sensitivity studies revealed a bacteriostatic end point of 5 units of penicillin, a bactericidal test indicated that the end point was more than 100 units for complete killing of the organisms. This perhaps explains why the first course of therapy was unsuccessful, when, with the antibiotic dosage employed, a total bactericidal effect was obtained only in the undiluted serum.

Probenecid was used in six cases. It was of apparent value in elevating the blood level penicillin in three of these cases. In the other three, use of the drug had to be discontinued after several days because of severe epigastric distress and heartburn, nausea and vomiting, and loss of appetite. In each of these three instances, the drug was given again after several days of freedom from symptoms; the same severe gastrointestinal distress recurred. The drug was given orally in doses of 0.5 Gm. every six hours.

Comment

Value of Combined Penicillin-Streptomycin Therapy. The clinical and experimental data presented by Hunter[53, 78] Jawetz and Gunnison[64] and Robbins and Tompsett[18] have indicated that penicillin and streptomycin in combination are the best antibiotic pair for the cure of enterococcal endocarditis in most instances. The data obtained from our study and from a review of the pertinent literature are in agreement with this concept. In vitro bactericidal tests with five of the strains of enterococci isolated in our cases indicated that the addition of bacitracin and erythromycin or other antibiotics to this combination is of little added value. Recent studies with the newer antibiotic, erythromycin, indicate that it is

ssentially a bacteriostatic agent for most rganisms and is bactericidal only for organisms ery sensitive to its action[76, 77]; in combination t behaves very much like the broad-spectrum ntibiotics. Bacitracin, on the other hand, is a predominantly bactericidal antibiotic and has been of value in the therapy of penicillin-resistant streptococcal and enterococcal endocarditis.

Inasmuch as the bactericidal antibiotics, penicillin and streptomycin, in combination, are very effective in the treatment of enterococcal endocarditis, the broad-spectrum antibiotics of the tetracycline group and chloramphenicol, erythromycin and carbomycin should not be used in the therapy of enterococcal endocarditis except in those rare instances in which they may enter into synergistic combination with a bactericidal antibiotic or pairs of antibiotics.

Hunter[22] has said that high doses of penicillin and streptomycin, 10 to 20 million units and 1 to 2 Gm. respectively per day, given in combination for a six-week period will usually cure most patients who have enterococcal endocarditis. He has stated succinctly the problem of the therapy of this valvular infection: "Ideally, the determination of the optimum treatment in penicillin-resistant infections should be based upon studies of the infecting organism recovered from each patient and these studies should include procedures which measure the bactericidal effects of the antibiotic tested." With this concept, we agree completely. Inasmuch as most enterococci are resistant to penicillin and since there is no way of knowing which patient with enterococcal endocarditis will respond to the above-mentioned program of therapy, it is perhaps wise to study each strain of enterococcus isolated from each patient. Each patient treated for enterococcal endocarditis represents a tremendous investment in time and money and work by a trained team of medical personnel. Since life may depend on a cure of the valvular infection with the first course of therapy, it would seem mandatory that therapy in these patients be guided by appropriate bacteriologic studies.

Value of Bactericidal Tests. Because of our experiences in a case of relapsing enterococcal endocarditis, we have attempted to correlate our therapeutic program in the last three cases with the results obtained from bactericidal tests employing the patient's organism and his serum containing the given antibiotics (cases 31, 32 and 33). In each instance, the daily dosage of penicillin was adjusted so that the penicillin-dihydrostreptomycin combination provided a bactericidal effect against the patient's infecting organism. Doses of 20, 20 and 50 million units of penicillin per day respectively, by continuous intravenous drip for these three patients together with 1 Gm. of dihydrostreptomycin every 12 hours gave a total bactericidal effect in dilutions of the patient's serum up to 1:8. We do not feel that this degree of bactericidal effect need be obtained in all treated patients. Adequate daily dosage of penicillin together with 2 Gm. of dihydrostreptomycin per day to provide a total bactericidal effect in the undiluted and the 1:2 dilution of serum should be curative in almost all instances when given for a six-week period. Too few patients with enterococcal endocarditis have been studied and treated in this manner to permit any final conclusions; however, it is quite possible that with a high degree of bactericidal effect during the entire course of therapy it may be possible to shorten the period of treatment for this type of valvular infection. Only further clinical trials with such bactericidal tests can indicate the optimal therapy for these patients.

Study of the results of penicillin therapy in this series of cases indicates that there is little correlation between the results of the in vitro inhibition tests and the outcome of treatment. It is unfortunate that the bactericidal end points were not obtained for all of the tested strains of enterococci as were the bacteriostatic end points. These data would have given us objective evidence of this lack of correlation. However, other studies[82] have indicated the marked differences between bacteriostatic and bactericidal end points for different strains of enterococci when penicillin is used. These differences undoubtedly account for failures of therapy when apparently adequate doses of penicillin are used and for instances of relapsing enterococcal endocarditis. This informa-

tion has necessitated the study, by means of bactericidal tests, of each strain isolated from patients with enterococcal endocarditis.

Current Program of Therapy. Use of Penicillin.—Our policy at present is to begin therapy, after the patient has been studied thoroughly, with 10 million units of aqueous penicillin-G by continuous drip per day through a plastic polythene needle or catheter. The next morning, the patient's serum is obtained to study the bactericidal effect of penicillin alone. Then treatment with dihydrostreptomycin, 1 Gm. every 12 hours, is started and the following morning, one hour after the injection of dihydrostreptomycin, serum is obtained for study of the combined effect of the two antibiotics. If a total bactericidal effect is obtained with a 1:2 or 1:4 dilution of the serum, then therapy is continued with the same dose of penicillin. If not, the penicillin is increased 10 or 20 million units and the bactericidal tests repeated. A maximal number of cured enterococcal valvular infections will be obtained in this way if the dose of penicillin is increased in amounts of 10 to 20 million units until a total bactericidal effect is obtained in a dilution of 1:2 or 1:4, regardless of what bacteriostatic or bactericidal end points are obtained by the in vitro tests.

Use of Streptomycin.—Treatment is started with 2 Gm. of dihydrostreptomycin since this is a moderately effective dose and can be continued for a reasonable period before signs of eighth-nerve toxicity appear. In case 30, 2 Gm. of dihydrostreptomycin was given for 10 weeks without any eighth-nerve impairment. In the last three patients treated, distrycin (a combination of equal parts of streptomycin and dihydrostreptomycin) was used with success. In case 31, it was used for 17 days without signs of toxicity. In case 32, we gave dihydrostreptomycin for three weeks, then instead of decreasing the dose to 1 Gm. per day as had been our custom, we gave distrycin for another three weeks for a total of six weeks of therapy without toxicity. In case 33, 2 Gm. of dihydrostreptomycin per day for nine days and 2 Gm. of distrycin per day for an additional 54 days for a total of nine weeks of therapy induced only slight loss of hearing and slight vestibular damage. Since distrycin apparently can be given for longer periods than either streptomycin or dihydrostreptomycin alone before toxicity appears, it should be the drug of choice in the long-term treatment of these individuals.[83] It is quite possible that most patients will be able to take combined streptomycin-dihydrostreptomycin in doses of 2 Gm. a day for six weeks with a minimum of eighth-nerve toxicity.

There is laboratory evidence to indicate that it would be preferable to continue the 2 Gm. dose of dihydrostreptomycin for the duration of therapy, barring any significant eighth-nerve damage. In vitro bactericidal tests in which the serum of patients receiving fixed amounts of penicillin but varying amounts of dihydrostreptomycin was tested against the same organism have shown that a greater bactericidal effect is obtained with the larger doses of dihydrostreptomycin.[21] The decision to continue distrycin in the 2 Gm. dose for a full six weeks or longer will depend on the patient's clinical response to therapy, the presence or absence of eighth-nerve symptoms and the results of audiometric and caloric tests.

Use of Probenecid.—Probenecid has been shown to increase the blood levels of penicillin significantly and is said to be of a low order of toxicity.[84] In enterococcal endocarditis in which large doses of penicillin need to be given to effect a cure, the use of this drug may contribute significantly to the elevation of the blood levels of penicillin and thus reduce the cost of therapy. In case 30, in which penicillin was given at the rate of 30 million units daily for 10 weeks, the blood levels of this antibiotic were almost constantly 64 units when checked from week to week, and occasionally varied from 32 to 128 units when 2 Gm. of probenecid was given in divided doses four times per day. No toxicity appeared from the prolonged use of the drug in this case. However, in three of the six patients in whom this drug was used, such pronounced and persistently severe gastrointestinal irritation occurred that the use of this medication was precluded.

With the use of probenecid we have obtained penicillin levels of as high as 256 units per milliliter of blood when 50 million units ha

been administered daily by continuous intravenous drip to a patient without renal insufficiency. With the ability to obtain such high levels of penicillin, the outlook for the patient with active enterococcal endocarditis should never be considered hopeless, barring death from incurable complications of the infection, even if many previous courses of therapy have been given. Additional courses of treatment, prefaced by appropriate bactericidal tests and with increasing doses of penicillin, together with probenecid, should be given these patients until a cure is achieved or death intervenes.

Prognosis. The average duration of the disease in these patients before antibiotic therapy was given at the clinic was six to seven months (range: one week to three years). This contrasts with active disease of three to four months' duration in penicillin-sensitive streptococcal endocarditis[85] before effective therapy was given. Among the 16 patients seen in the last three years, there have been four deaths. In all four of these cases, active disease had been present 7 to 36 months.

Prognosis is definitely related to the duration of active endocarditis before adequate antibiotic therapy is given. With effective and curative bactericidal antibiotics for the treatment of enterococcal endocarditis and with early diagnosis, this valvular infection should be arrested in almost all cases, and mortality from active disease and its ensuing complications ought to be at a minimum. Within the short span of a decade, a seemingly hopeless infection carrying a high mortality rate even with penicillin therapy has been brought under control. The rate of cure of enterococcal endocarditis now approximates that obtained with endocarditis caused by the penicillin-sensitive "viridans" streptococci. The total cure rate for the group made up of our last 16 patients was 75 per cent; the corrected cure rate, calculated on the basis of 14 patients who were treated adequately for an appropriate interval, was 86 per cent.

Infections on Normal Valves. In this series it was possible to establish the nature of the underlying heart disease in about half of the cases. There was a definite history of rheumatic fever in 10 cases and a questionable history of this disease in another case. There was a history of a heart murmur before the onset of bacterial endocarditis in 18 cases. In the remaining 15 cases of the series, however, there was no history of rheumatic fever or chorea, heart disease or a heart murmur prior to the time the valvular infection was acquired. In at least 6 of these 15 cases, cardiac examinations by the home physician (three cases) and previous examinations at the Mayo Clinic (3 cases) had not revealed any evidence of heart disease or a heart murmur. In one patient (case 19) there apparently had been active endocarditis for some 10 months without a history of fever or chills before admission to the clinic; the patient was afebrile and without a heart murmur for the first two weeks of hospitalization, but then a heart murmur became obvious and led to the diagnosis of endocarditis.

In 16 cases it was felt that rheumatic heart disease was the determinative background for the valvular infection, and in two cases a congenital cardiac lesion was present. In nine of the cases, it was difficult to say whether the mitral or aortic valve was involved; loud systolic murmurs were heard over most of the left precordial area, these murmurs often being loudest at the apical area. While in most instances these murmurs would turn out to be the result of mitral valve involvement, on a statistical basis a few would probably be found to be aortic in origin.

In none of the six cases in which necropsy was performed was there a history of previous heart disease or heart murmur prior to the onset of the endocarditis. In one of these cases necropsy revealed a bicuspid aortic valve, while in the other five there was no apparent underlying cardiac lesion except the vegetations and changes attributable to bacterial endocarditis. These limited data suggest that in most of the 15 cases in which there was no previous history of heart disease or heart murmur the infection probably attacked previously normal valves. Support for this thesis is obtained by a review of the reported cases of enterococcal endocarditis in which necropsy was performed and a definite statement was made regarding the presence or absence of underlying

heart disease.[1-5, 17, 18, 27, 29, 32, 35, 45-49, 59, 61, 86-88] Twenty-five of 39 fatalities, including the six in our series of cases, apparently represented infections of normal valves, giving a rate of more than 60 per cent. This figure is at variance with the currently accepted opinion that subacute bacterial endocarditis rarely affects the normal valve. In 25 of 37 cases of enterococcal endocarditis reviewed in 1942[14] the underlying cardiac lesions were given on the basis of clinical or anatomic evidence; of these, 20 represented rheumatic heart disease, four arteriosclerotic heart disease and one syphilitic valvular disease.

Antibiotic Prophylaxis. Half of the enterococcal infections in our series of cases resulted from transurethral operations or instrumentation. In half of these, in turn, there was no antecedent history of heart disease or heart murmur. Since enterococcal endocarditis may develop after urologic operations or instrumental manipulation in patients with or without heart murmurs, antibiotic prophylaxis assumes a very important role in their management. Since enhanced bactericidal effect is observed with combined penicillin-streptomycin for most strains of nonhemolytic streptococci, it would seem that this combination would constitute the best prophylactic therapy for patients who are to undergo urologic operations. We have employed 2 million units of penicillin and 2 Gm. of dihyrostreptomycin per day given in divided doses every 12 hours beginning the day before operation and continuing postoperatively until one day after the urethral catheter has been removed. One million units of penicillin and 1 Gm. of dihyrostreptomycin are administered one or two hours before the surgical procedure in order to give maximal antibiotic blood levels at the time of operation. We have not seen enterococcal or other forms of endocarditis develop when this antibiotic prophylactic program has been carried out preoperatively in patients with or without a heart murmur.

It has been recommended that larger doses of penicillin combined with 2 Gm. of dihydrostreptomycin be given prophylactically to patients who are to undergo transurethral prostatic resection.[62] No evaluation of this antibiotic combination for prophylaxis before urologic operations has yet been published, but it would seem that the smaller doses recommended above would be adequate. Studies are under way to determine the value of antibiotic prophylaxis in connection with transurethral prostatic resection.[89]

Summary and Conclusions

Thirty-three unselected cases of enterococcal endocarditis encountered during the first decade (January, 1944, through December, 1953) of antibiotic therapy for bacterial endocarditis are reported. Sixteen patients were seen in the last three years of this period. Thirty-one of the 33 patients were treated with antibiotics. Sixteen patients (48 per cent) died from their infection or from complications of active endocarditis. Seven of the treated patients (22 per cent) were cured with penicillin alone. Of the 16 patients seen in the last three years, four died, giving a cure rate of 75 per cent. However, two of these patients died without antibiotic therapy and two died from cerebral embolism while they were under adequate combined antibiotic therapy. Hence, the corrected cure rate was 86 per cent (12 of 14 patients). Ten of these patients were cured with combined penicillin-dihydrostreptomycin therapy and two with penicillin alone. The cure rate in enterococcal endocarditis now approximates that obtained in endocarditis caused by penicillin-sensitive streptococci.

Probenecid was helpful in three of six patients who received combined therapy. However, in three patients, severe epigastric distress and heartburn necessitated the stopping of treatment with the drug.

In vitro bactericidal tests performed with five strains of enterococci isolated from these patients indicated that penicillin and dihydrostreptomycin constituted the most effective pair of antibiotics for bactericidal effect. The addition of erythromycin or bacitracin to the penicillin-dihydrostreptomycin combination did not give any greater killing effect.

Therapy of enterococcal endocarditis should be individualized. The daily dosage of penicillin and the duration of therapy should be governed by the results of bactericidal tests in which the

patient's serum containing the antibiotics is employed against the patient's strain of enterococcus. A greater number of cures will be achieved in this way.

Inasmuch as enterococcal endocarditis follows urologic procedures quite frequently, it is recommended that all such patients with or without a heart murmur be given a million units of penicillin and 1 Gm. of streptomycin or dihydrostreptomycin every 12 hours beginning the day before operation and continuing postoperatively until the day after the urethral catheter has been removed. We have not known enterococcal endocarditis to complicate urologic manipulation when this antibiotic prophylactic program has been followed.

The data indicate that in more than half the cases of enterococcal endocarditis the infection apparently attacked a normal heart valve. Further clinical and postmortem studies are needed to clarify this finding.

Sumario Español

Treinta y tres casos no seleccionados de endocarditis enterocócica encontrados durante la primera década (Enero, 1944 hasta Diciembre, 1953) de terapia antibiótica para la endocarditis bacterial son informados. Treinta y uno de los 33 pacientes fueron tratados con antibióticos. Diez y seis (48 por ciento) murieron de la infección o de complicaciones de la endocarditis activa. Siete de los pacientes tratados (22 por ciento) fueron curados con penicilina solamente. De los 16 pacientes vistos en los últimos tres años, 4 murieron, produciendo un promedio de 75 por ciento de curas. Sinembargo, 2 de estos pacientes murieron sin terapia antibiótica y 2 murieron de embolismo cerebral mientras estaban bajo terapia antibiótica combinada. Así es que el promedio de casos curados corregido fué de 86 por ciento (12 de 14 pacientes). Diez de estos pacientes fueron curados con combinaciones de penicilina-dihidroestreptomicina y 2 con penicilina solamente. El promedio de cura en la endocarditis enterocócica ahora se aproxima al de endocarditis causada por estreptococos penicilino-sensitivos.

La probenecida fué provechosa en tres de seis pacientes que recibieron terapia combinada. Sinembargo, en tres pacientes, malestar severo epigástrico y pirosis impidió la continuación del uso de la droga. Pruebas bactericidas en vitro hechas en cinco cepas de enterococos aislados en estos pacientes indicaron que la penicilina y dihidroestreptomicina constituyeron el par de antibióticos más efectivo en cuanto a efecto bactericida. La adición de la eritromicina o bacitracina a la combinación de penicilina-dihidroestreptomicina no produjo un aumento en el efecto bactericida.

La terapia de la endocarditis enterococica se debe de individualizar. La dosis diaria de penicilina y la duración de la terapia debe ser gobernada por los resultados de pruebas bactericidas en las cuales el suero del paciente conteniendo los antibióticos se emplea contra la cepa de enterococo. Un mayor número de curas se puede obtener de esta manera.

Como la endocarditis enterocócica frecuentemente complica procedimientos urológicos, se recomienda que todos estos pacientes con o sin soplos cardíacos se les administre un millón de unidades de penicilina y 1 gramo de estreptomicina o dihidroestreptomicina cada 12 horas empezando el día antes de la operación y continuando postoperativamente hasta el día después de haberse removido el catéter uretral. Nosotros no hemos tenido conocimiento de endocarditis enterocócica complicar procedimientos urológicos cuando este programa antibiótico profiláctico ha sido instituido.

Los datos indican que en más de la mitad de los casos de endocarditis enterocócica la infección aparentemente atacó una válvula cardíaca normal. Más estudios clínicos y de autopsia se necesitan para clarificar este hallazgo.

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The Dynamics of the Heart in Complete A-V Block

An Angiocardiographic Study

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The conduction disturbances in atrioventricular block are well known from numerous electrocardiographic studies, but the effect on the heart work, especially on the individual chambers, could not be recorded before the introduction of visualization of the heart chambers by angiocardiography. Rapid biplane angiocardiography with simultaneous electrocardiographic yields information on cardiac dynamics not available by procedures with a purely static anatomic perception.

IN complete atrioventricular block the atria and ventricles contract independently and the relationship of the atrial to the ventricular contractions is always changing. This type of dissociation offers a unique opportunity to study the mode of action of the atria and the ventricles independently and in various combinations.

Interesting clinical and pathophysiologic observations in complete atrioventricular block have been contributed by electrocardiography, phonocardiography and phlebography, and by pressure curves obtained by heart catheterization.[1, 2] However, the contributions of angiocardiography to the study of this condition has not been reported previously. A discussion of the supplementary information on the dynamics of the heart which this method of study may supply is the purpose of this paper.

ANGIOCARDIOGRAPHIC TECHNIC USED IN THE PRESENT INVESTIGATION

The technic of the angiocardiographic method has been reported elsewhere.[3] Seventy per cent Umbradil was injected as contrast medium. The patients were sedated with a 2.5 per cent solution of Avertin by rectum, the dosage being 0.1 ml. per kilogram of body weight. Children remained quiet with shallow respiration during the examination.

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CASE REPORT

Case 1. A female infant weighing 3100 Gm. was born at term on May 6, 1947 after an uneventful pregnancy and delivery. There was no cyanosis but persistent dyspnea and lethargy. Mental development was normal, but the child did not walk until the age of 18 months and was never able to be very active. On May 28, 1950, the infant girl was found unconscious in bed and taken immediately to a hospital where she had about 30 generalized convulsions always preceded by loss of consciousness. The seizures were controlled after three days with barbiturates and ephedrin.

Soon thereafter the child was admitted to this clinic for further investigation. At the age of 3 years and 3 months her weight was only 9.5 Kg. and height 88.5 cm. Exertional dyspnea but no cyanosis was present. Physical examination showed the heart to be enlarged to the left and slightly to the right; the point of maximum impulse was in the sixth left intercostal space in the nipple line. A long, rather soft systolic murmur was heard over the precordium, maximal in the third left intercostal space 1 cm. to the left of the midsternal line. The rhythm was regular, the rate 70 per minute. The second pulmonic sound was accentuated. The femoral pulse was normal. Two days after admission a sudden change in the rhythm of the heart developed when it became completely irregular with a rate of 35 to 45 beats per minute.

Electrocardiogram and phonocardiogram revealed complete A-V block with a ventricular rate of 45 per minute. The QRS complexes were normal and there was no axis deviation. The S-T segments were slightly depressed in leads I and II, and the T waves were positive in the three conventional leads. At the apex the phonocardiogram revealed a systolic murmur in the frequency range of 50 to 1000 vibrations per second with the maximal amplitude in early systole. Over the pulmonary valve was recorded a systolic and diastolic murmur in the same frequency range.

An x-ray film of the chest showed generalized cardiac enlargement with a volume of 490 cc. per square meter of body surface area.

Angiocardiography was performed on Aug. 26, 1950, with injection of the contrast substance into the right antecubital vein. Left and right anterior oblique projections were taken simultaneously. The superior vena cava was normal and all the heart chambers were dilated. No right-to-left or left-to-right shunt was demonstrated.

No further evidence of the Adam-Stoke's syndrome occurred during the hospital stay. The cardiac rhythm continued to be slow and irregular; it was not affected by ephedrin. Circulation time (fluorescin) from the right antecubital vein to the lips was 10 seconds, a normal value.

The dynamics of the right heart in complete atrioventricular block are illustrated by the accompanying angiocardiograms shown in figure 1.

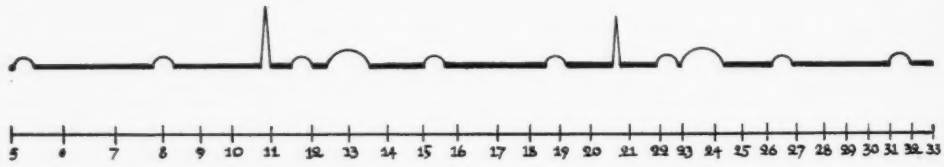

FIG. 1.

The time of each exposure after the injection of Umbradil is indicated. These times are also shown on the semischematic electrocardiogram.

Exposure 5. The right atrium is in late diastole and right ventricle in early diastole, immediately after the T wave. The contrast medium is rapidly filling the ventricle.

Exposure 6. This exposure shows the end of the first of the two atrial systoles preceding the ventricular contraction. The ventricle is still poorly visualized, indicating that it is dilated and already partially filled with blood. Note the complete emptying of the atrium and its appendage.

Exposure 7. The heart is again in diastole. Traces of the contrast substance are seen in the inferior vena cava, probably because of the rapid injection of the contrast medium.

Exposure 8. Early atrial systole, the second preceding the ventricular systole is demonstrated. Since the ventricle is already practically filled, the atrial emptying is much more difficult. This is indicated by a heavy true reflux into the inferior vena cava, the orifice of which is normally functionally closed during atrial systole. The atrial appendage is already empty.

Exposure 9. The ventricle is still poorly visualized after two atrial contractions, and the atrial appendage is filled again.

Exposure 10. The heart is in diastole. The right atrium has increased little in size, and the reflux into the inferior vena cava has not disappeared.

Exposure 11. As soon as the right ventricle starts to contract, the right atrium increases suddenly in size, and the contrast medium in the superior and inferior vena cava streams into the atrium. In diastole the right atrium can be seen to be moderately enlarged.

Exposure 12. Atrial and ventricular systole coincide. The atrioventricular valves do not open, but there are heavy refluxes into the inferior and superior venae cavae and the sinus venosus. The atrium decreases little in size. The pulmonary artery is considerably dilated.

Exposure 13. In early atrial diastole the atrium increases somewhat in size, and the contrast medium, forced back into the afferent veins by the reflux, is returning to the atrium.

Exposure 14. Immediately at the end of ventricular systole the right ventricle fills rapidly and almost completely before atrial systole occurs. (Compare with the filling effect of the first atrial systole, 6.) The contrast substance in the caval veins and sinus venosus has simultaneously returned to the atrium. (Note there is an interval of ½ second between 13 and 14.) The caliber of the inferior vena cava and the hepatic veins has decreased.

Exposure 15. The ventricle is well filled up to the pulmonary valves in spite of the fact that no effective atrial systole has occurred since the last ventricular systole. The atrium has diminished in size.

Exposure 16. The atrium does not decrease much in size when it does contract. A reflux into the inferior caval vein is seen again. The ventricle is much enlarged in diastole. The fact that the size of the atrium decreased more during the systole visualized in 5 and 6 may be due to the circumstance that this systole occurred earlier in ventricular diastole, before the ventricle was so well filled.

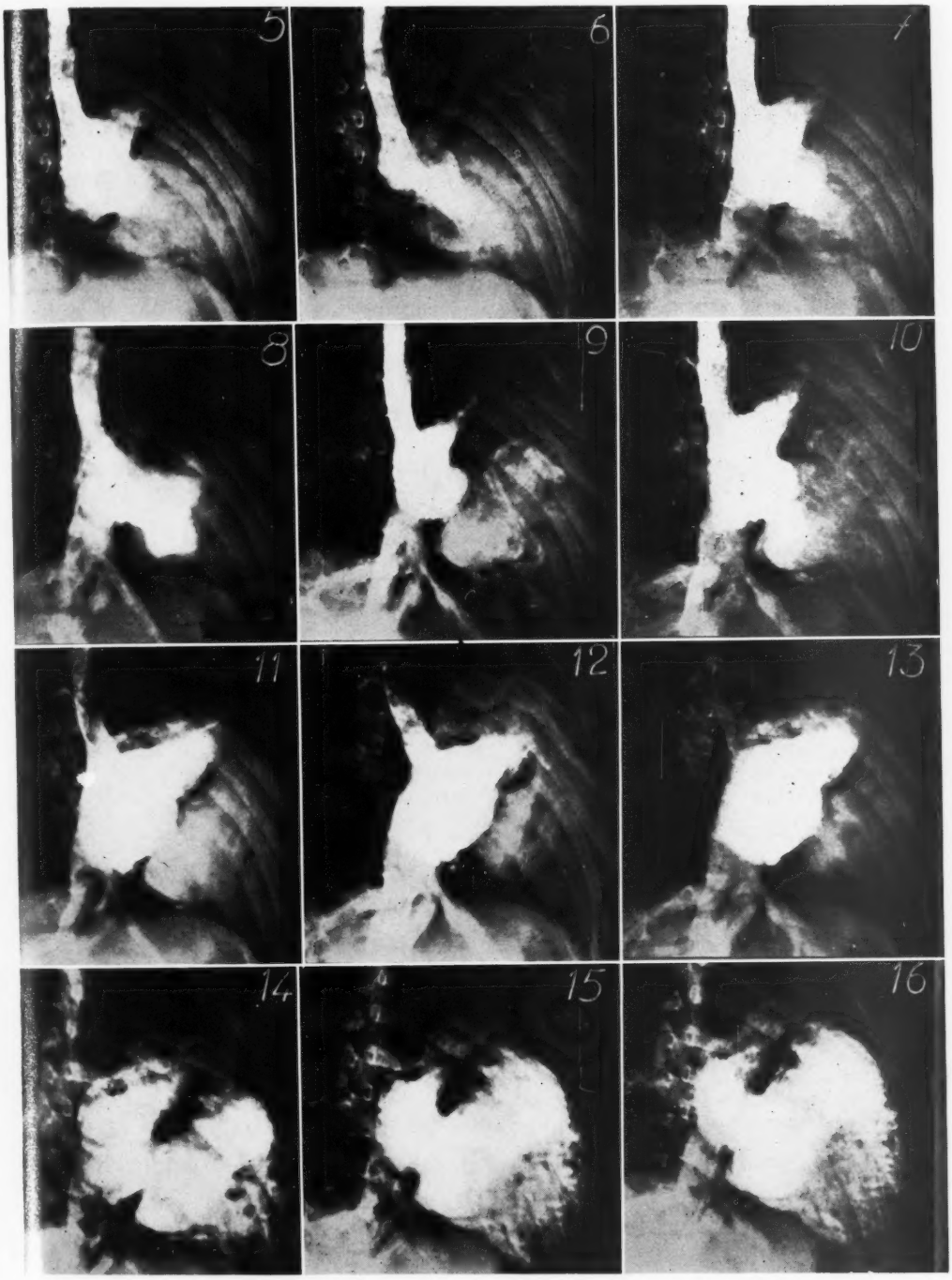

FIG. 1. See legend on facing page.

Angiocardiography performed on the seventeenth day of life in another patient with complete heart block revealed the same findings but less dilatation of the cardiac chambers.

Discussion

The atrium empties very effectively when the atrial contraction occurs immediately after the T wave, for then the ventricle is virtually empty and the ventricular pressure is low (exposures 5, 6). The later in ventricular diastole the atrial systole occurs, the less complete is the emptying of the atrium. (Compare exposures 26 and 27 with 5 and 6 and 15 and 16.) When the atrium contracts for the second time during ventricular diastole, it is difficult to force more blood into the already well-filled ventricle, because the atrioventricular pressure difference is small. Since emptying is less effective, the atrium diminishes little in size, and the contrast medium is forced into the inferior vena cava, indicating increased intra-atrial pressure. If the atrium begins to contract during ventricular systole, the atrioventricular valve fails to open, and the resulting increased atrial pressure results in a reflux of blood into all the afferent veins (exposures 12 and 23).

The ventricle fills rapidly as soon as the atrioventricular valves open. The diastolic filling of the ventricles, even without atrial systole, takes much less time than the systolic emptying. At the same time the atrium diminishes markedly in size without having contracted (exposures 13, 14, 15). During the latter part of diastole neither the right ventricle nor the right atrium changes visibly in size.

The sequence of pictures 20, 21, 22 and 23 demonstrates the great systolic dilatation of the pulmonary artery, which results from the

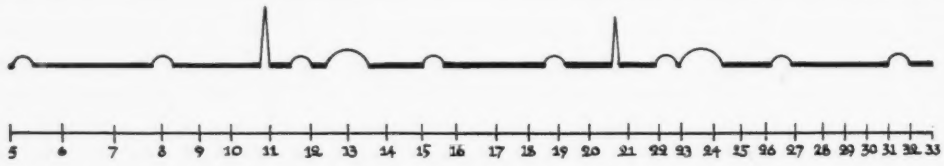

Fig. 1 (*continued*)

As in figure 1 the time of each exposure after the injection of Umbradil is indicated. These times are also shown on the semischematic electrocardiogram.

Exposures 17 and 18. In spite of a prolonged atrial diastole the atrium does not increase markedly in size probably because the distended ventricles nearly fill the pericardial sac and prevent complete atrial dilatation.

Exposure 19. Atrial systole, occurring when the ventricle is almost maximally filled, forces a reflux of contrast medium into the inferior vena cava. Since the ventricle is too full to contain more blood, the atrium apparently diminishes in size, particularly the atrial appendage.

Exposure 20. The atrial appendage has refilled and the atrium is slightly larger.

Exposure 21. Early ventricular systole dilates the pulmonary artery. The right atrium fills simultaneously.

Exposure 22. During ventricular systole the pulmonary artery increases markedly in caliber. The right atrium is now larger than it ever was during diastole.

Exposure 23. Again an atrial systole occurs during the ventricular contraction with consequent reflux into the venae cavae and the sinus venosus. The atrioventricular valves do not open and the atrium maintains the approximate former size.

Exposure 24. The end of ventricular systole demonstrates increased residuum in the ventricle. The pulmonary artery remains dilated in spite of the fact that the ventricle is now in the phase of reduced ejection.

Exposure 25. The ventricle has resumed its diastolic size and shape and is already well filled. Now the pulmonary artery decreases in caliber.

Exposure 26. The right atrium is now smaller in full diastole.

Exposure 27. The atrium is still smaller in systole. The pulmonary artery and its main branches have finally resumed their narrow diastolic caliber.

Exposure 28. In atrial and ventricular diastole the right atrium is virtually stationary in size. During ventricular diastole the pulmonary artery slowly assumes a more curved configuration.

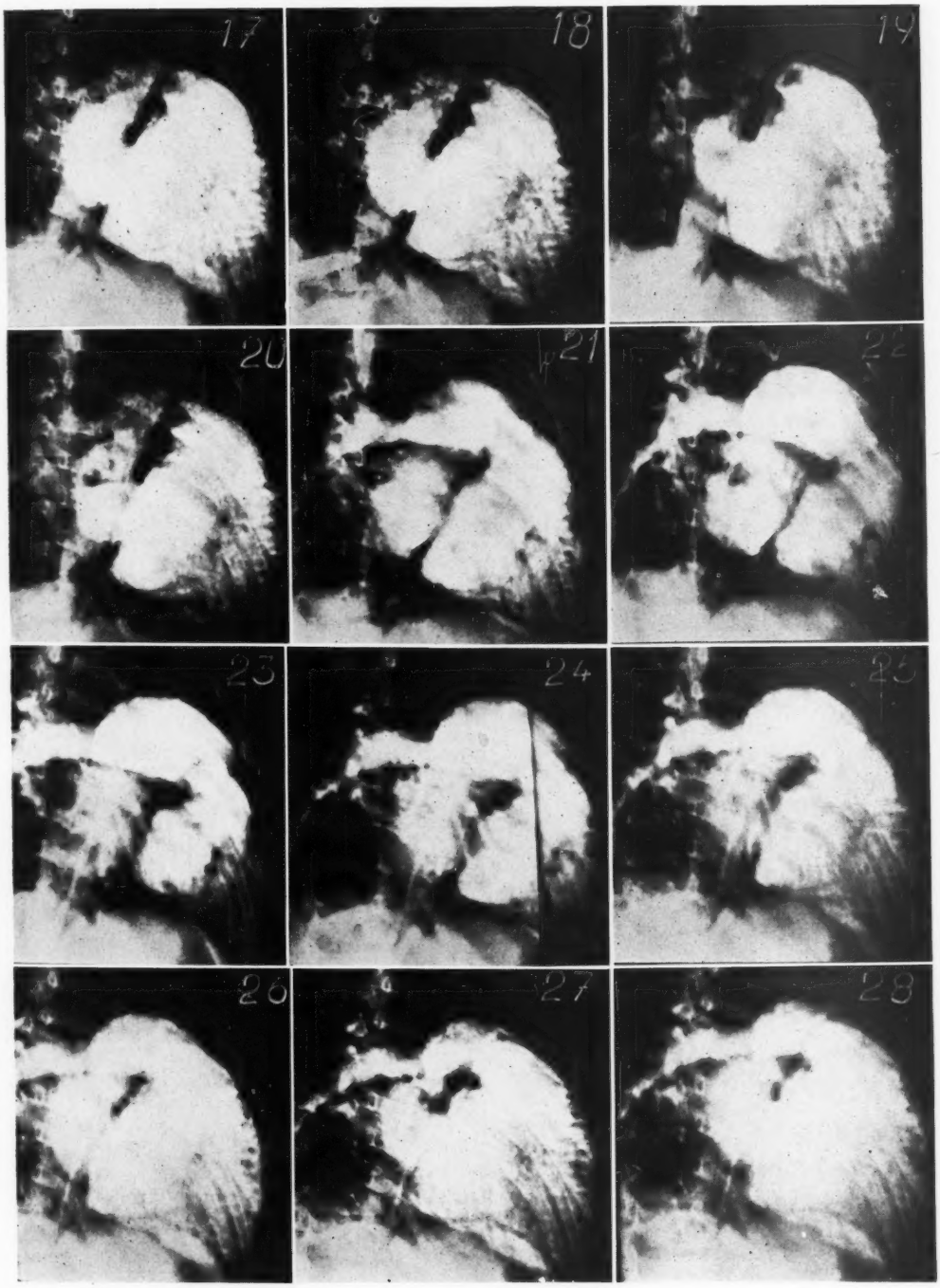

FIG. 1 (*continued*). See legend on facing page.

increased stroke volume with bradycardia. Maximal diameter is reached in picture 22 and is maintained during the entire systole, not only during rapid ejection but even throughout the phase of reduced ejection. The dilatation, however, is functional and disappears gradually during diastole.

In addition to the change in size, there is also a change in shape, with a straightening of the normal curve of the pulmonary artery during ventricular systole. In spite of the fact that the complete heart block has existed for more than three years in this patient, the pulmonary artery is slender in diastole and does not appear to be organically dilated.

The above description of the dynamics of the right heart during complete atrioventricular heart block applies equally well to the left heart. There is comparable reflux into the pulmonary veins when the atrium cannot empty into the ventricle; it is less strikingly demonstrated, however, because of dilution of the contrast medium in the lesser circulation.

Summary

The cardiac dynamics in complete atrioventricular heart block have been studied by means of rapid biplane angiocardiography with simultaneous electrocardiography. The method permits the study of the mechanism of contraction of the separate heart chambers.

Sumario Español

La dinámica cardíaca en el bloqueo atrioventricular completo ha sido estudiada por medio de angiocardiografía de biplano rápido con electrocardiografía simultanea. El método permite el estudio del mecanismo de contracción de las cámaras separadas del corazón.

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Lowering of Serum Cholesterol by the Administration of a Plant Sterol

By MAURICE M. BEST, M.D., CHARLES H. DUNCAN, M.D., EDWARD J. VAN LOON, PH.D., AND JOAN D. WATHEN, B.S.

The plant sterol, beta-sitosterol, has been administered to nine subjects on unrestricted diet. A sustained reduction of serum total cholesterol and a lowering of the ratio of cholesterol to lipid phosphorus occurred. Interference by sitosterol with the absorption of cholesterol, both dietary and that excreted into the gastrointestinal tract, is presumably responsible for this hypocholesterolemic effect. No toxic or undesirable side effects were observed. A means of studying the effects of a sustained lowering of serum cholesterol on atherosclerotic states would now seem to be available.

THE sitosterols are the most widely distributed of the plant sterols, or phytosterols. This sterol fraction is now known to contain at least five components, alpha$_1$, alpha$_2$, alpha$_3$, beta, and gamma sitosterols.[1] Beta and gamma sitosterols, the most extensively studied members of the group, are stereoisomers and differ only in the spatial configuration of the C-17 side chain. Beta-sitosterol is the main sterol of cottonseed oil, tall oil, and wheat-germ oil; gamma-sitosterol is the principal sterol of soybean oil.[2]

Beta and gamma sitosterols are closely related to cholesterol in chemical structure (fig. 1), but differ in that they are not appreciably absorbed from the digestive tract.[3] Peterson and co-workers have studied the effects of the administration of sitosterol to chicks maintained on high fat and high cholesterol diet. They noted a markedly lower plasma and liver level of cholesterol[4] and a highly significant decrease in the incidence of atherosclerosis.[5] This was interpreted to indicate that sitosterol interferes with the absorption of cholesterol. A lowering of serum cholesterol in human subjects fed a usual diet plus crude soy sterol, presumably largely gamma sitosterol, has been reported.[6]

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METHODS

Nine subjects were selected for treatment. Two (Subjects H-1 and H-2) had serum cholesterol levels within the normal range and were without evidence of cardiovascular or renal disease. Seven patients were hypercholesterolemic. Included were three with previous myocardial infarction (patients H-3, H-6, H-7), two with chronic renal disease (patients H-8, H-9), one with peripheral vascular disease (patient H-4), and one with a labile hypertension (patient H-5). A major factor in the selection was the willingness of the subjects to cooperate and adhere to the schedule of treatment.

Beta-sitosterol was administered orally in dosage of 5 to 6 Gm. immediately before the ingestion of food. There was no restriction as to type or amount of food. The preparation was in liquid form, 30 ml. containing 3 Gm. of 98 per cent pure beta sitosterol. A placebo preparation, similar in appearance, taste, and consistency, was also employed in the study. At no time did the patient know whether he was taking sitosterol or placebo, and the majority remained unaware that a placebo was ever used. This precaution was taken to avoid possible influence of such knowledge on the patients' selection of diet, particularly with regard to fat and cholesterol content. To minimize the chance of other possible bias the initial eight weeks of the study were conducted by the double-blind method, in which neither subject nor doctor knew which preparation was sitosterol and which was placebo.

The period of study ranged from 13 to 29 weeks, with an average of 22 weeks. Included were two periods of placebo administration in all patients, and one or more periods of sitosterol administration. All determinations of serum cholesterol are included in the data presented except those during the two-week period immediately after discontinuation of

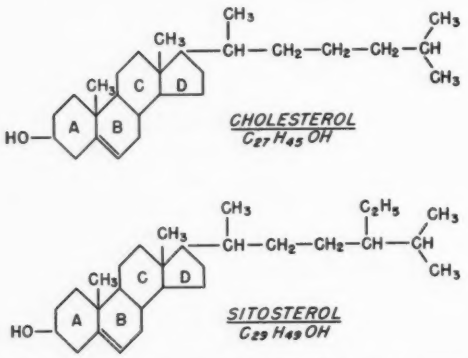

FIG. 1. The structural formula of beta and gamma sitosterols differs from that of cholesterol only in the presence of an ethyl group on carbon-24.

TABLE 1.—*Effect of Beta-Sitosterol on Serum Total Cholesterol (Abell)*

Subject	Mean Serum Total Cholesterol (*mg./100 ml.*)		% Fall	Probability
	Control	Treatment		
H-1	196 ± 11	183 ± 10	6.7	<.05*
H-2	215 ± 10	199 ± 16	7.9	.10
H-3	260 ± 11	230 ± 14	11.6	.02*
H-4	261 ± 17	223 ± 16	14.7	.01*
H-5	270 ± 10	241 ± 13	10.7	.05*
H-6	283 ± 6	248 ± 12	12.1	.001*
H-7	305 ± 3	249 ± 23	18.1	.02*
H-8	276 ± 4	240 ± 13	13.1	.01*
H-9	1122 ± 35	898 ± 200	20.0	.02*

* Significant at 5 per cent point value for n − 1 degrees of freedom.

sitosterol. These values were omitted in order to minimize any possible persistent sitosterol effects on the placebo values.

The patients were seen at weekly intervals, their weight recorded, and a fasting specimen of blood drawn at approximately 9 a.m. Serum was separated by centrifugation. Independent determinations of serum total cholesterol were made in duplicate by three methods, that of Abell,[7] and modified versions of those of Pearson,[8] and Zlatkis.[9] Lipid phosphorus was determined by the method of Zilversmit.[10] Selected sera were subjected to flotation analysis by the ultracentrifuge.

RESULTS

Table 1 summarizes the effects of beta-sitosterol administration on serum total cholesterol (Abell) in the nine subjects. In all there was a reduction in serum total cholesterol, the

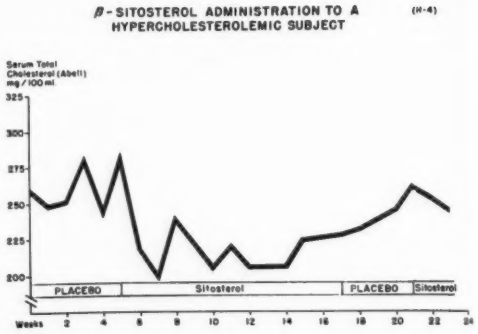

FIG. 2. A fall in serum total cholesterol is noted during beta sitosterol administration, with return to the initial range when a placebo was substituted. The concentrations of S_f 10-30 and 30-100 classes of lipoproteins at the end of 7 and 12 weeks of sitosterol administration were approximately one-half those during the placebo period. This subject has continued to take sitosterol, and at 31 weeks his serum total cholesterol is 212 mg. per 100 ml.

mean fall ranging from 13 to 224 mg. per 100 ml. In terms of per cent of control level, the fall ranged from 6.7 per cent to 20.0 per cent. Eight of the nine patients showed a reduction in cholesterol significant at the 5 per cent point value or below, as determined by the *t* test.

Changes in serum total cholesterol during alternate periods of placebo and sitosterol administration in patient H-4 are shown in figure 2. Apparently spontaneous fluctuations in the serum cholesterol during the initial placebo and sitosterol periods emphasize the necessity for repeated determinations in studies of this type.

A consistent difference was noted in absolute values of serum total cholesterol by the three methods employed. Figure 3, showing the hypocholesterolemic effect of sitosterol administered to patient H-6, illustrates this difference. The parallelism demonstrated by this patient was noted in all subjects.

The hypocholesterolemic effect of sitosterol is manifest at the end of one week, but there is further decline during the succeeding four weeks of administration (fig. 4). No tendency toward "escape" has been noted, and at the end of up to 18 weeks of continuous administration the cholesterol level has remained below control levels.

Significance of the mean difference of paired

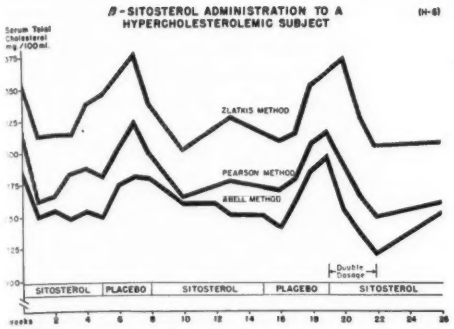

FIG. 3. Ultracentrifuge studies of the serum of this subject were performed at the fifteenth and nineteenth weeks. The rebound in serum cholesterol during the second placebo period was accompanied by an approximate doubling of the concentration of S_f 10–30 and 30–100 classes of lipoproteins.

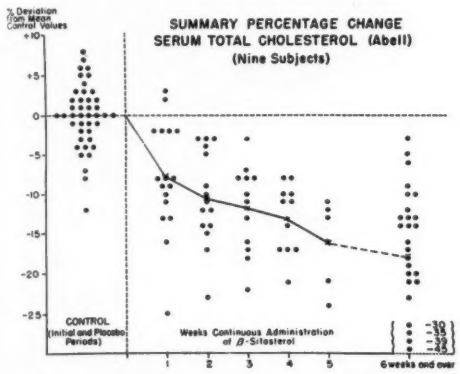
% Deviation from Mean Control Values
SUMMARY PERCENTAGE CHANGE
SERUM TOTAL CHOLESTEROL (Abell)
(Nine Subjects)
CONTROL (Initial and Placebo Periods)
Weeks Continuous Administration of β-Sitosterol
6 weeks and over

FIG. 4. Percentage lowering of serum total cholesterol in nine subjects. Note absence of any tendency to "escape."

values (mean control and mean sitosterol for each patient) is shown in table 2 for each cholesterol method. The per cent reduction will be seen to be quite similar by all three, although the absolute reduction is somewhat greater as measured by the method of Zlatkis. In our laboratory the method of Abell gives results in good agreement with Schoenheimer-Sperry; the modified methods give higher values, that of Pearson about 30 mg. per 100 ml., and that of Zlatkis about 63 mg. per 100 ml. The reduction of serum total cholesterol of 12.8 per cent is based on all determinations made during sitosterol administration. As can be seen from figure 4, the reduction would be appreciably greater if determinations during the first two weeks of sitosterol administration were eliminated.

TABLE 2.—*Mean Reduction Serum Total Cholesterol*

Method	mg./100 ml.	%	Probability
Abell	53.0	12.8	$<.001$
Pearson(mod.*)	56.5	12.0	.001
Zlatkis(mod.*)	63.3	11.9	.001

* To be published.

A less significant reduction ($p < .02$) in the ratio of serum total cholesterol to lipid phosphorus was observed in the nine patients. In three patients (H-2, H-4, and H-7) the fall in the ratio of 20.4, 25.6, and 16.2 per cent, respectively, was statistically significant. The reduction in the ratio of serum total cholesterol to lipid phosphorus was due largely to the fall in serum total cholesterol, lipid phosphorus showing no consistent change.

Lipoprotein concentrations were determined by means of the ultracentrifuge at the completion of placebo and sitosterol treatment periods in patients H-4, H-6, and H-7. In these patients the concentrations of S_f 10–30 and 30–100 classes of lipoproteins at the end of the period of sitosterol administration were approximately one-half that of the placebo period.

DISCUSSION

The level of plasma cholesterol would seem to be regulated by a rather efficient homeostatic mechanism, ordinarily varying only within narrow limits. This relative constancy is the result of a dynamic equilibrium rather than the existence of plasma cholesterol as a stagnant pool. The average life of a molecule of plasma cholesterol (regeneration time) is approximately 12 days.[11] Thus cholesterol is continuously being excreted or metabolized, and replaced by either synthesis or absorption.

Although most tissues have been shown to be capable of synthesizing cholesterol from acetate, the liver appears to be the only appreciable source of endogenous plasma cholesterol, at least in the dog.[12] It has been estimated that the hepatic synthesis of cholesterol in man is about 1.2 Gm. per day.[13]

The cholesterol content of the average Amer-

ican diet varies from a low value of 0.2 to 0.3 Gm. per day to a high of 0.7 to 0.8 Gm., depending upon the foods ingested.[14] Dietary cholesterol, being derived from cellular material, is largely in the free (non-esterified) state. The mechanism of cholesterol absorption is incompletely understood, but there is some evidence that esterification by pancreatic esterase is involved.

Cholesterol presented to the gut for absorption includes not only that in the diet, but also the estimated 0.5 to 1.5 Gm. excreted daily by the liver. The cholesterol in the bile is in the same free state as that in the diet,[15] and there is no reason to suspect that the gut differentiates between cholesterol molecules from these two sources.

From these considerations it seems probable that a substance which interferes with the absorption of cholesterol would act upon both dietary cholesterol and that present in the bile. The effects of sitosterol administration would thus not necessarily be the same as those of restriction of dietary cholesterol.

The mechanism by which sitosterol interferes with the absorption of cholesterol has not been established. Pollack has proposed that the admixture of sitosterol and cholesterol results in the formation of nonresorbable crystals.[16] Hernandez and associates have reported that in rats sitosterol interferes with the esterification of cholesterol, and suggest that this effect may be responsible for the interference with absorption.[17] The time relationship of the administration of sitosterol to ingestion of food is important; administration immediately before meals facilitates admixture of the plant sterol with the cholesterol in the food and that contained in the bile.

Schoenheimer has presented direct evidence that the plant sterols are not absorbed in experimental animals,[18] but the evidence that beta sitosterol is not absorbed in man is as yet indirect. The cholesterol methods used all give color development with beta-sitosterol. As compared with the optical density given by an equal amount of pure cholesterol, that of beta sitosterol has been determined to be 60.5 per cent by the method of Abell, 71.5 per cent by that of Pearson, and 79 per cent by that of Zlatkis. Furthermore, in vitro addition of beta-sitosterol to serum reveals no interference with color development, the optical density being the exact sum of those obtained when the cholesterol in the serum and the added beta-sitosterol are determined separately. Any appreciable absorption of beta-sitosterol thus seems unlikely, in view of the observed fall in serum cholesterol, as determined by these methods.

The sustained lowering of serum cholesterol by dietary means alone is difficult. Keys has shown that the fall in serum cholesterol is dependent upon the absence of both cholesterol and neutral fat from the diet.[19] Such a rigid dietary regimen is unacceptable to patients for any prolonged period. Failure to achieve a sustained lowering of serum cholesterol by dietary means may also be due to an increase in endogenous cholesterol production by the liver or intestinal mucosa. It has been shown by Gould and Taylor that the level of exogenous cholesterol ingestion inversely influences the rate of endogenous synthesis from acetate in the dog and rabbit.[20]

Preliminary results of studies now in progress indicate that the administration of beta-sitosterol is accompanied not only by a lowering of serum total cholesterol, but also by changes in other serum lipids, A decrease in the level of the "atherogenic" S_f 10–100 classes of lipoproteins and a fall in serum neutral fat[21] have been noted in the subjects so studied. Gofman has observed a reduction in S_f 12–100 classes of lipoproteins in some subjects following limitation of caloric intake or of fat in the diet.[22] The changes incident to sitosterol administration cannot be attributed to negative caloric balance, since weight loss did not occur. Whether or not there is any interference with fat absorption remains to be determined.

The administration of beta-sitosterol has not been accompanied by toxic reactions or undesirable side effects. The preparation is not unpleasant and is suitable for long-term administration. While the evaluation of any measure directed toward atherosclerosis is a difficult problem because of the lack of criteria

for determining the extent or rate of progression of the disease, beta-sitosterol would seem to offer a means of testing the value of a sustained reduction in serum cholesterol.

Conclusions

1. The administration of beta-sitosterol to human subjects on an unrestricted diet is accompanied by a significant reduction in serum total cholesterol.

2. The ratio of serum total cholesterol to lipid phosphorus is reduced following the administration of beta-sitosterol. The reduction is due largely to the change in cholesterol, since lipid phosphorus is not consistently altered.

3. A reduction in the "atherogenic" S_f 10–100 classes of lipoproteins has been observed in the three subjects whose serums have been studied by the analytic ultracentrifuge.

4. Toxic or unpleasant side effects have not been observed in subjects receiving sitosterol.

5. Beta-sitosterol, by interfering with the absorption of dietary cholesterol and with the reabsorption of that excreted into the gastrointestinal tract, offers a means of studying the effects of a sustained lowering of serum cholesterol in atherosclerotic states.

Sumario Español

1. La administración de beta-sitosterol a sujetos humanos en una dieta no restringida fué acompañada por una significativa reducción en el colesterol total del suero.

2. La proporción del colesterol total del suero al fósforo lípido se reduce luego de la administración del beta-sitosterol. La reducción se debe grandemente al cambio en colesterol ya que el fósforo lípido no se altera consistentemente.

3. Una desviación de la clases S_f 10–100 "aterogénica" de lipoproteinas fué observado en los tres sujetos cuyos sueros fueron estudiados por la ultracentrífuga analítica.

4. Efectos tóxicos o indeseables no han sido observados en los sujetos durante la administración del sitosterol.

5. El beta sitosterol ofrece un medio de estudio para los efectos de una reducción sostenida del colesterol del suero en sujetos ateroescleróticos, mediante la interferencia a la absorción del colesterol dietético y en la reabsorción de aquel eliminado en el tubo digestivo.

Acknowledgment

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The Clinical Determination of Mitral Insufficiency when Associated with Mitral Stenosis

By O. Henry Janton, M.D., Guenther Heidorn, M.D., Louis A. Soloff, M.D., Thomas J. E. O'Neill, M.D., and Robert P. Glover, M.D.

A review of 200 consecutive operated cases of pure mitral stenosis and 47 consecutive operated cases of mitral stenosis with an associated mitral insufficiency indicates that careful evaluation of the history, auscultatory findings, electrocardiogram and fluoroscopy permits a correct diagnosis of associated insufficiency in a majority of instances. History and auscultation remain the internists' most valuable tools despite a large array of as yet incompletely evaluated mechanical measures.

IT HAS BEEN OBSERVED that the presence of severer degrees of mitral insufficiency associated with mitral stenosis increase operative mortality amd morbidity and decrease the number of worthwhile operative results.[1] The detection of this associated lesion is at times difficult and frequently not made except by the surgeon's exploring finger in the left atrium.

This study is a review of 247 consecutive case histories taken from our first 500 patients who have undergone mitral commissurotomy. It is an attempt to determine clinical features which might aid in the detection of an associated mitral insufficiency.

Methods and Materials

Two hundred consecutive operated cases of pure mitral stenosis and 47 consecutive operated cases of mitral stenosis with associated mitral insufficiency are included in this series.

The presence or absence of insufficiency was determined in every case by finger palpation of the mitral valve and subjectively grading the regurgitant jet of blood from 0 to grade 4. We are aware of the crudeness of using the palpating finger of the surgeon in the left atrium for the diagnosis of mitral regurgitation. However, the many variable mitral valve configurations prevent precise quantitative determination of the degree of regurgitation by any method available today. Only patients with a regurgitant jet of grade 2 or more as determined by this method were included in the category of associated insufficiency.

Thirty-two of the 47 patients with mitral stenosis and insufficiency had a jet of grade 2 intensity; 11 were of grade 3; only four were of grade 4 intensity. No cases of pure mitral insufficiency were encountered in this series.

The transverse diameter of the orifice of the mitral valve bore no apparent close correlation to the severity of the regurgitant stream striking the palpating finger. The orificial opening in these 47 patients varied from one cigarette in diameter to three fingers. A combination of factors such as flexibility of valve leaflet and of chordae tendineae, papillary muscle contractility and the position of the mitral valve orifice relative to the left ventricular outflow tract probably are as significant as the cross sectional area of the mitral inlet.

This paper will be primarily concerned with the evaluation of those procedures available to the average clinician, namely, the history, auscultatory findings, the electrocardiogram and x-ray.

Clinical Features

Natural History. The clinical course of the average patient with *pure* mitral insufficiency differs strikingly from that of the patient with *pure* mitral stenosis. In mitral insufficiency the history is one of relative benignity. Dyspnea, an early disabling symptom of mitral stenosis, occurs later and is overshadowed by the primary complaint of easy fatigability in mitral insufficiency. Chronic disability is often postponed until the fifth or sixth decade in pure insufficiency unless subacute bacterial endocarditis or episodes of acute rheumatic fever supervene. This is probably due to the fact that

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there is little or no sustained pulmonary hypertension until late in the course of this disease. Other reports have noted a dominance of males[2, 3] and a lessened incidence of a positive rheumatic fever history in patients with mitral insufficiency as compared with patients who have mitral stenosis.[2, 4, 5]

However, as will be noted throughout this report, these apparently clear-cut differences vanish under the influence of an associated mitral insufficiency and stenosis. As the two lesions relinquish their purity and combine, the more dynamic pathophysiology of mitral stenosis usually dominates the clinical picture and thereby complicates the clinical differentiation.

There was no appreciable age difference in our two groups of patients, although 40 per cent of those with associated insufficiency were males as compared with 25 per cent with pure stenosis. A positive rheumatic fever history was obtained in 40 per cent of the patients with pure mitral stenosis, and in 70 per cent of those with an accompanying insufficiency. This is contrary to the reported findings in pure mitral insufficiency.

Fatigue played a more dominant role than did exertional dyspnea when the severer grades of incompetence were present. This was true both early and late in the symptomatic course of such patients.

Strikingly, systemic arterial embolization occurred much less frequently when mitral regurgitation is associated with mitral stenosis. It occurred in 23.5 per cent of those patients with pure stenosis but in only 6.4 per cent of those in whom regurgitation was also present.[6] Apparently, the regurgitant jet prevents stagnation of blood, and hence thrombus formation in the left atrium. It is usual at operation to find a left atrium free of thrombi if significant regurgitation is associated with mitral stenosis, and this was noted in 43 of the 47 cases. This was also true even in the presence of atrial fibrillation (19 of 24 patients). In pure mitral stenosis, however, a thrombus was found in the left atrium in 86 of 200 patients. Subacute bacterial endocarditis may be the source of arterial emboli in some of those patients who had no thrombi in the left atrium but had a positive history of systemic arterial embolization. It has often been noted that the incompetent mitral valve is more susceptible to the ravages of endocarditis than the purely stenotic one.[5, 7, 8, 9]

Auscultation. The characteristic murmur of dynamically significant pure mitral insufficiency is usually best heard at the mitral area. It is usually rough, grade 3 or 4 in intensity and holosystolic (less frequently late systolic) in time. It begins with the first heart sound and frequently dampens or obscures it. The murmur extends up to and includes the second sound or the aortic component of a split second sound. Its transmission is usually laterally to the axilla and back but less well to base of the heart. The pulmonic second sound may be accentuated. A third heart sound easily mistaken for the opening snap of mitral stenosis is often heard in pure mitral insufficiency. Systolic murmurs which originate at the aortic valve may occasionally be heard only at the mitral area. Differential auscultatory features are: (1) these aortic murmurs start later in systole and therefore do not include the first sound, (2) they are accentuated in mid-systole, and (3) they rarely include the second sound.

A systolic murmur of varying intensity at the mitral area was heard in 30 per cent of patients who had only a pure mitral stenosis. Thus, we see that the clinician is frequently challenged as to the significance of a mitral systolic bruit. The greater the similarity between the murmur heard and the characteristic murmur of pure mitral insufficiency the more likely that it is indicative of a dynamically significant associated mitral incompetence. The intensity of the murmur is the most important single factor. None of the patients with pure mitral stenosis had a mitral systolic murmur of grade 4 intensity, although six of the 200 had one of grade 3. Contrastingly, a grade 3 or 4 murmur was heard in 13 of 15 patients who had a regurgitant jet of grade 3 or 4 associated with stenosis.

Scarring and calcification of the anterior leaf of the mitral valve is a common cause of mitral systolic murmurs in pure stenosis. Turbulence is created by the irregular surface as the blood is ejected along the left ventricular

outflow tract, striking the scarred anterior mitral valve leaf and passing through the aortic valve. Fifteen of 25 patients with pure stenosis who had a systolic murmur of grade 2 or more demonstrated a calcified anterior mitral valve leaf at surgery.

X-ray Examination. X-ray films offers only limited aid in the differentiation of pure and impure mitral stenosis. The great difficulty of detecting left ventricular enlargement by x-ray, especially in the presence of a marked right ventricular enlargement, has been generally realized. Mitral insufficiency exerts relatively minor dynamic effects upon the left ventricle and enlargements of this chamber are usually minimal, if present at all. The left ventricle was found to be minimally (1+) enlarged at operation in only 7 of the 15 patients with an associated regurgitation of grade 3 or 4.

Massive (aneurysmal) dilatation of the left atrium is usually considered to be caused by mitral stenosis with an associated insufficiency,[10, 11] although it is felt by some to be more characteristic of pure mitral stenosis.[12] Thirteen massively dilated left atria were found at surgery in this series. Eleven of these had an associated regurgitation (nine of grade 3 or 4). However, two exhibited only pure stenosis.

Systolic expansion of the left atrium as seen upon fluoroscopy in multiple views has been thought to be caused by systolic regurgitation of blood into the left atrium. It has been extensively studied by many authors[13-16] but unfortunately this phenomenon has proved to be of little clinical value because it is frequently seen in pure mitral stenosis.

Calcification of the mitral valve was demonstrated at operation in 65 per cent of our 47 patients with associated regurgitation, and in 32 per cent of those with pure stenosis.

Electrocardiogram. A pattern of left ventricular hypertrophy is seldom seen in patients with mitral stenosis and associated mitral insufficiency. Only one patient with associated regurgitation demonstrated this pattern as an isolated finding and it was combined with right ventricular hypertrophy in only two other patients. Nor is the absence of a right ventricular hypertrophy pattern on the electrocardiogram in the presence of a clinically evident mitral stenosis suggestive of associated mitral insufficiency. The absence of right or left ventricular hypertrophy was noted in 98 of our 200 patients with pure stenosis. Also, 9 of the 15 patients with severe associated insufficiency had right ventricular hypertrophy upon their electrocardiograms.

Summary of Additional Graphic Aids in the Diagnosis of Mitral Insufficiency Associated with Stenosis

Numerous mechanical measures have been utilized in attempting to diagnose mitral insufficiency associated with mitral stenosis. These are not readily available to the average clinician and consequently will be discussed only briefly. In general, these procedures have proven of only limited value, even in experienced hands, as compared with the clinical stand-bys of auscultation and natural history. There is great need for more extensive correlation with surgical findings before these procedures can be properly evaluated.

Cardiac Catheterization. It was hoped that pressure curves obtained by "wedging" the catheter tip into the smaller capillary branches of the pulmonary artery would accurately reflect the pressures of the pulmonary venous system and the left atrium. If this were true it would be of great aid in detecting the systolic surge of blood into the left atrium which is present in mitral insufficiency. There is, however, a great deal of dispute among investigators as to whether these "wedge pressure curves" actually reflect pressure changes in the left atrium. Some authors[17] feel that they do not.

Auricular Esophagogram. Luciani[18] first noted the existence of cardiac pulsations when an inflated balloon was placed in the esophagus at the level of the left atrium. Minkowski[19] and Rautenberg[20] described a positive plateau curve obtained in systole in cases of mitral insufficiency. However, recent work, notably that of Abelmann[16] and others, has shown the poor correlation of these curves with the surgical findings.

Left Auricular Electrokymograms. Electrokymography of the heart was introduced by

Boone, Henny and Chamberlain[21] in 1947. It was applied to the left atrial border by Luisada and Fleischner[22] in 1948 and a positive systolic plateau was obtained in the presence of mitral insufficiency. But the same authors found similar tracings in cases of clinically pure mitral stenosis. Soloff[23] reported detailed observations of the findings of electrokymography in mitral regurgitation. It was his conclusion that this laboratory aid was not as useful as detailed fluoroscopy of the heart in skilled hands. In addition, he stresses that the normal heart can and frequently does produce records identical to those seen in mitral insufficiency. Recently curves of like nature were found in persons with normal hearts and in those with pure mitral stenosis, proved at operation.[16]

Phonocardiograms. Margolies and Wolferth[24] showed that in mitral stenosis the time interval between the second heart sound and the opening snap of the mitral valve in the presence of atrial fibrillation varied with the preceding cycle length. Messer and co-workers[25] and Weiss and Joachim[26] noted a varying time interval between the onset of electrical systole and the first heart sound in similar patients again depending on the previous cycle length. Recently an interesting and perhaps quite important observation was made by Kuo and Schnabel.[27] They observed that these two intervals remained fixed when there was an associated mitral or aortic insufficiency. Their observations up to this time have been limited to only a small number of cases.

Ballistocardiogram. The ballistocardiogram has only recently been used as a possible aid in the diagnosis of mitral insufficiency. It has been reported that a consistent headward ballistic wave occurs preceding the J wave when mitral insufficiency is present.[28] There has again been too little clinical correlation to justify any conclusions as to its value.

Direct Left Atrial Pressure. An ingenious method of obtaining direct pressure readings from the left atrium by bronchoscopic passage of a needle through the right main bronchus has recently been reported.[29] Further correlation is again needed.

Conclusions and Summary

Although pure mitral insufficiency and pure mitral stenosis appear to be two separate clinical entities, their apparently clear-cut dissimilarities are quickly lost when the two are combined. Mitral stenosis is the dynamic dominant and soon governs the clinical picture. However, certain dissimilarities remain to varying degrees in the individual patient and are useful in their clinical evaluation. Preoperative detection of severer grades of mitral insufficiency associated with mitral stenosis is important. It has been observed that these patients have an increased operative morbidity and mortality as well as a lessened degree of worthwhile postoperative results as compared with patients with only pure mitral stenosis.

It has been observed upon reviewing 200 consecutive operated cases of pure mitral stenosis and 47 consecutive operated cases of mitral stenosis with an associated mitral insufficiency that careful evaluation of the natural history, auscultatory findings, electrocardiogram and fluoroscopy permits a correct diagnosis of associated insufficiency a majority of the time. History and auscultation remain the internists' most valuable tools despite a large array of as yet incompletely evaluated mechanical measures.

Thirty per cent of 200 patients with a pure mitral stenosis had a mitral systolic murmur in addition to a diastolic murmur. It is in this group that the question of significant associated insufficiency arises. The intensity of the mitral systolic murmur is the most useful differential feature of auscultation. Thirteen of 15 patients with a regurgitant jet of grade 3 or 4 as determined by the palpating finger in the left atrium had a systolic murmur of grade 3 or 4 intensity. No grade 4 systolic murmurs were heard in pure mitral stenosis although 6 of these 200 patients did have a murmur of grade 3 intensity. In addition, it can be generally stated that the greater the similarity to the characteristic murmur of pure mitral insufficiency the more likely that such a systolic murmur is indicative of a dynamically significant regurgitation.

Further clinical aid can be gained by obtain-

ng a chronologic and complete history of the disease. Systemic arterial embolization occurs much less frequently when insufficiency is associated with mitral stenosis than when stenosis exists alone. It occurred in 23.5 per cent of the 200 patients with pure stenosis but only 6.4 per cent when regurgitatoin was also present. This decided difference was also noted when auricular fibrillation accompanied mitral insufficiency and stenosis. Apparently, the regurgitant stream prevents stagnation of blood and thrombus formation in the left atrium.

Fatigue rather than dyspnea usually plays the early dominant role in the symptomatology of those patients with severe associated insufficiency. Apparently, sustained pulmonary hypertension with its deleterious effects on the right heart and upon the lungs occurs later in such individuals than in those with pure stenosis and thereby delays the onset of dyspnea.

The only value of the electrocardiogram in the differentiation of the predominance of mitral stenosis versus mitral insufficiency is the presence of left ventricular hypertrophy when insufficiency is predominant. In such cases in our experience mitral valve commissurotomy has failed to produce beneficial results; in fact, such patients developed a significant mitral regurgitation after surgery, which inevitably results in death from congestive heart failure. About one-half of all patients with pure mitral stenosis showed no electrocardiographic evidence of right ventricular preponderance, at the time of surgery. The relatively small dynamic effect of mitral insufficiency upon the left ventricle is reflected not only in the electrocardiogram, but also by noting a normal-sized left ventricle demonstrated fluoroscopically and directly observed at operation.

In our experience massive dilatation of the left atrium with mitral stenosis and insufficiency indicates that the insufficiency is of dynamic significance. Of eleven patients in whom preoperative clinical diagnoses of massively dilated left atria were confirmed at operation, 9 had a regurgitant jet of grade 3 or 4. It was interesting that the two other patients with massively dilated left atria were found in the 200 cases with pure mitral stenosis.

It is evident from the foregoing that there is no single clinical or laboratory procedure that will predict the predominance of mitral insufficiency over mitral stenosis. Rather, it is a matter of integrating the historical and laboratory features of each patient.

Sumario Español

Un repaso de 200 casos consecutivos operados de estenosis mitral pura y 47 casos operados consecutivos de estenosis mitral asociada con insuficiencia mitral indica que la evaluación cuidadosa del historial, los hallazgos auscultatorios, electrocardiograma y fluoroscopía permiten el diagnóstico correcto de insuficiencia asociada en la mayoría de los casos. La historia y la auscultación persisten como los medios más valiosos para el internista no obstante el gran número de aún poco evaluadas medidas mecánicas.

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Anticoagulant Therapy with Dicumarol Maintained during Major Surgery

By STEN MÜLLERTZ, M.B., AND OLE STORM, M.B.

Most postoperative thromboses are probably initiated before or during surgical interventions and most of the fatal embolisms occur during the early postoperative period. As a complete prophylaxis, Dicumarol therapy was begun before, and maintained at an effective level during and after, major surgical interventions in 11 patients with a marked thromboembolic predisposition. No excessive hemorrhage, thromboembolic incidents or other unusual complications were encountered. The precautions necessary for a safe performance of the procedure are described.

ANTICOAGULANT therapy with Dicumarol has been shown to reduce the incidence of thrombosis and embolism and has been used prophylactically after surgical interventions.[1] In these cases the Dicumarol treatment was started during the first two postoperative days and became effective only some days later. However a large proportion of the fatal, postoperative pulmonary embolisms occur in this early period[2]; and it is probable, that most postoperative thromboses are initiated before or during surgery. Therefore prophylaxis with Dicumarol against thromboembolic complications in surgery can be complete only when instituted before, and maintained during and after surgery. In some papers the results of Dicumarol treatment after surgical operations,[3-6] after delivery,[7, 8] during emergency operations,[9, 10] in experimental surgery,[11] and during some forms of vascular surgery[12] have suggested that no risk of uncontrollable hemorrhage should be expected in a properly administered Dicumarol therapy during surgery. In a small group of surgical patients with a strong thromboembolic predisposition and a bad general physical condition, the risk of hemorrhage by continuous treatment with Dicumarol was preferred to the risk of thromboembolism.

It is the aim of the present paper to demonstrate that a Dicumarol treatment can be maintained before, during, and after major surgery without increased hemorrhage or other complications when the treatment is carefully controlled by a reliable and sensitive method.

METHOD

Dicumarol produces a decrease in the level of proconvertin (factor VII) and prothrombin in blood.[13] The effect of the treatment was followed by a one-stage assay of the combined effect of proconvertin and prothrombin[13] as described by Astrup, Müllertz and Rud Hansen.[14] A saline buffer extract of human brain, stored at −20 C. was used as thromboplastin. Oxalated ox plasma, freed from prothrombin and proconvertin by adsorption and stored at −20 C., supplied proaccelerin (factor V) and fibrinogen. Plasma from oxalated human blood (9 volumes blood + 1 volume potassium oxalate, 2 per cent) was diluted 1:10 with a buffer-oxalate-saline mixture. In test tubes 0.2 ml diluted plasma, 0.2 ml thromboplastin, and 0.2 ml adsorbed ox plasma were mixed and recalcified at 37 C. with 0.2 ml of a calcium chloride solution (optimal concentration, approximately 30 mM.). The clotting times were converted into percentages of normal by interpolation on a correlation graph prepared from dilutions of a mixture of several normal plasma samples. The advantages and accuracy of this method have been studied.[15] The usual prothrombin tests, in which a dried thromboplastin reagent and undiluted plasma are used, are less reliable,[14, 15] and were not considered safe enough for our purpose.

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Procedure

A reduction of the thromboembolic morbidity is generally obtained when the proconvertin-prothrombin level is kept below 30 per cent of the normal value.[1] Below 5 per cent, there is an increased risk of major hemorrhage, above 10 per cent the risk is small.[16] It was planned to induce an initial fall in proconvertin-prothrombin to a level of 10 to 20 per cent. A level between 20 and 30 per cent on the day of operation was considered desirable. Generally the treatment was begun four to six days before operation to allow time for the determination of the approximate maintenance dose of Dicumarol. After operation the level was maintained between 10 and 30 per cent until the patient was effectively ambulatory (two to four weeks). Dicumarol tablets of 20 mg. were used to allow changes in dose of 10 mg. (= one half tablet). Accidental low levels could be corrected to therapeutic and safe levels by oral administration of 50 mg. of menadione sodium bisulfite.[17] In case of severe hemorrhage a safe level could be reached quickly by transfusions of fresh blood and by intravenous administration of 250 to 500 mg. of vitamin K_1 in a water emulsion.[18, 19]

In the dosage of Dicumarol[16] attention was given the delayed response (one to two days), the protracted cumulative effect (about two days for small doses, five to seven days for large doses), and the large individual variations in tolerance. As it is difficult to foretell the response of any patient to Dicumarol, 300 to 400 mg. Dicumarol were given during the first two days, and the subsequent dosage

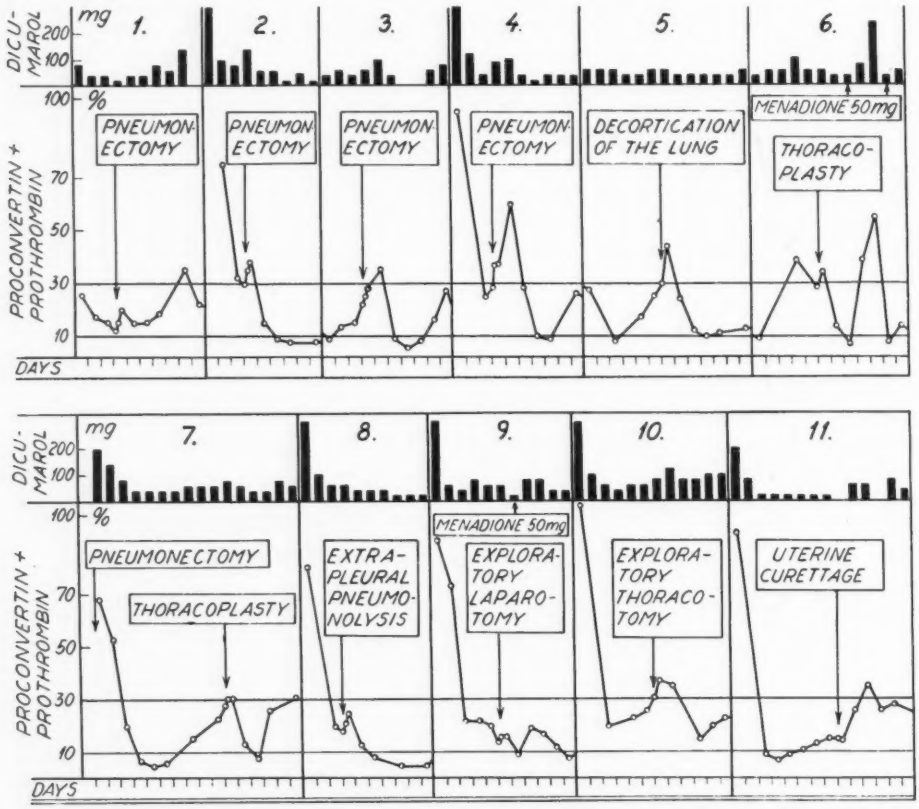

Fig. 1. The dosage of Dicumarol and the proconvertin-prothrombin level in blood before, during, and after surgical interventions in 11 cases (see case reports). The daily doses of Dicumarol (in milligrams) are shown in the upper parts, the proconvertin-prothrombin-levels (in per cent of the normal level) in lower parts of the chart. The horizontal lines at 10 and 30 per cent indicate the therapeutic range for an effective antithrombotic prophylaxis without risk of hemorrhage. The time of operation is indicated with arrows. The proconvertin-prothrombin level was determined immediately before, during, and one to three hours after the operation, in cases 6, 10, and 11 only, before and after the operation.

was determined by the response to the first doses, and to the expected postoperative decrease in the proconvertin-prothrombin level. (See below.)

The transient rise in the level during the operation (fig. 1), was caused by the proconvertin and prothrombin of the transfused blood. This had no apparent effect on the level of the next day and was left out of consideration in the planning of the dosage.

Observations

The Postoperative Decrease in Proconvertin-Prothrombin Level

The proconvertin-prothrombin levels of the 11 patients treated with Dicumarol in the days before, during, and after the surgical intervention (indicated by arrows) are shown in figure 1. During our investigation it became obvious that the proconvertin-prothrombin level decreased markedly in the early postoperative period. This was especially pronounced in cases 5 and 7, in which Dicumarol doses of the same magnitude were followed by increasing levels before, and decreasing levels after the operation. The decrease did not occur in cases 10 and 11. In most cases the Dicumarol doses were reduced or withheld in the postoperative period (cases 2, 3, 4, 6, 8, 9) and in two cases menadione (50 mg doses) was administered orally with immediate but variable effects (cases 9 and 6).

The proconvertin-prothrombin level was followed in a number of patients undergoing similar surgical interventions without Dicumarol treatment. A definite postoperative decrease was observed in three patients (fig. 2, cases 1, 3, 4), a small decrease in two patients (fig. 2, cases 2 and 5), while no significant change was observed in case 6. These results are in accordance with those of Warren and Belko.[20]

The postoperative decrease may be caused by an increased consumption and/or a decreased production of these factors and may be associated with a lowered tolerance to Dicumarol.

The individual variations of the postoperative decrease make the dosage difficult during and after the operation. The establishment of a level between 20 and 30 per cent during the operation and a reduction of the Dicumarol doses on the day before and on the day of operation are now considered to be important precautions against dangerously low postoperative levels.

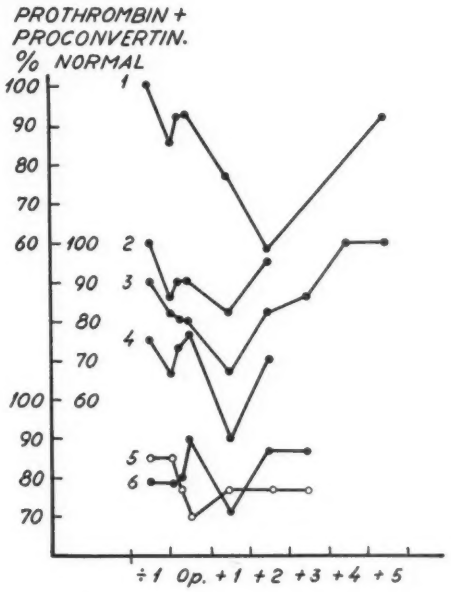

Fig. 2. The proconvertin-prothrombin blood level was determined before, during, and after exploratory thoracotomy (cases 1, 2, 3 and 4) and pneumonectomy (cases 5 and 6) for cancer of the lung. No Dicumarol treatment. Abscissa: Days before and after operation. Ordinate: Upper part, case 1; middle part, cases 2, 3 and 4; lower part, cases 5 and 6.

Clinical Results

Dicumarol treatment was administered to 11 patients who were predisposed to postoperative thromboembolism. The predisposition was caused by different factors known to produce a high incidence of thromboembolism:[1] nine of our patients had had previous thromboembolic episodes and five had degenerative heart disease (two with previous coronary occlusion). Three of our patients had marked generalized arteriosclerosis, five had cancer of the lung and seven had chronic infections. One was obese, four were 60 years of age or older and six were in very bad physical condition. In nine patients extensive

surgical operations made the postoperative mobilization less effective. In six patients surgery of the lung exposed the patient to an increased release of thromboplastin into the blood.

The following surgical interventions were performed during Dicumarol therapy: Pneumonectomy in four patients; exploratory thoracotomy in one patient; thoracoplasty in two patients; extrapleural pneumonolysis in one patient; decortication of the lung in one patient; uterine curettage (therapeutic abortion) in one patient; exploratory laparotomy (large incision for gastrectomy) in one patient.

The dosage of Dicumarol and the proconvertin-prothrombin level in the days before, during and after operation are shown in figure 1. During the operation it was about 30 per cent in six patients (cases 2, 4, 5, 6, 7, 10), between 20 and 30 per cent in two patients (cases 3, 8) and between 10 and 20 per cent in three patients (cases 1, 9, 11). The amount of hemorrhage during the operation was evaluated by two experienced surgeons. In thoracic surgery large vessels and large muscles are transsected and especially in thoracoplasty, extrapleural pneumonolysis, and decortication of the lung hemostasis cannot be complete. Any abnormal bleeding should be easily discovered in thoracic surgery and in uterine curettage. The postoperative hemorrhage in thoracic surgery was evaluated from the volume of the fluid collected by drainage and aspiration from the thoracic and extrapleural cavities. The normal postoperative hemorrhage and the normal amount of blood transfused in a series of similar operations are shown in table 1.

TABLE 1.—*Normal Amount of Transfused Blood and of Postoperative Hemorrhage in Thoracic Surgical Interventions*

Operation	No. of cases	Transfused blood (ml.) average	Postoperative hemorrhage (ml.)		
			average	5 cases below	5 cases above
Pneumonectomy	50	2500	1520	750	2750
Exploratory Thoracotomy	50	1000	570	100	2770
Extrapleural Pneumonolysis	50	1000	700	300	800
Thoracoplasty	50	1000	560	100	1355

Transfused blood: The amount transfused during the operation and the first 24 hours. The postoperative hemorrhage was determined from the amount of blood collected by drainage and aspiration.

Case Reports

The amount of blood transfused during operation and the hemorrhage during and after operation were normal or below normal average, when not expressly otherwise stated. The postoperative courses were uneventful except in cases 4 and 8. No deaths occurred.

Case 1. This male patient, 55 years of age, had cancer of the lung, hypertension, arteriosclerosis, coronary sclerosis and a history of a previous attack of coronary occlusion. During pneumonectomy 1500 ml. blood were transfused and the blood loss was 700 ml. (estimated by weighing). The postoperative hemorrhage was 1210 ml. The patient was treated with Dicumarol for nine days before and 24 days after operation.

Case 2. This patient, a man 62 years of age, had cancer of the lung, arteriosclerosis, myocardial degeneration and a previous attack of coronary occlusion. During pneumonectomy 1500 ml. blood were transfused. The postoperative hemorrhage was 680 ml. The patient was treated with Dicumarol for four days before and 34 days after operation.

Case 3. This man, 57 years of age, with cancer of the lung and previous attacks of thrombophlebitis, also suffered from extensive varicose veins of both legs. Dicumarol treatment was initiated, and high ligation of the saphenous veins was performed. Pneumonectomy was performed seven days later during Dicumarol therapy. During operation profuse bleeding (approximately 800 to 1000 ml.) occurred through a tear in the pulmonary artery. The total blood loss during the operation was 1500 ml. (estimated by weighing); 2000 ml. blood were transfused during operation and 1000 ml. blood after the operation (normal 2500 ml., table 1). Apart from this, no abnormal bleeding was observed. The postoperative hemorrhage was 1570 ml. The patient was treated with Dicumarol for eight days before and 11 days after operation.

Case 4. This patient, a woman 59 years of age, had cancer of the lung, syphilis, angina pectoris and degenerative heart disease. During pneumonectomy 1500 ml. blood were transfused; five hours after operation the patient went into shock and 2000 ml. blood were transfused (normal 2500 ml., table 1). At this time the proconvertin-prothrombin level had increased above 37 per cent and the hemorrhage was

not abnormal. The total amount of hemorrhage through the pleural drain was normal (1300 ml.). The patient was treated with dicumarol for three days before and 11 days after operation.

Case 5. This man 67 years of age, suffered from empyema, hypertension, arteriosclerosis, and pericarditis. A large thrombophlebitis of the left leg was treated with Dicumarol. The symptoms disappeared, and 18 days after initiation of treatment decortication of the lung was performed. During the operation 1000 ml. blood were transfused. The postoperative hemorrhage was 490 ml. Later a purulent secretion was discharged through the drain. The hemorrhage was not unusual as compared with 7 similar operations. The hemorrhage in these patients was difficult to evaluate because of the empyema. The patient was treated with Dicumarol for 17 days before and 19 days after operation.

Case 6. This female patient, 38 years of age, had tuberculosis of the lungs. A left extrapleural pneumonolysis was performed without Dicumarol treatment and a thrombosis of the left axillary and brachial vein occurred seven days after the operation. Dicumarol was immediately administered with good effect and maintained during thoracoplasty on the right side 12 days later. During this second operation 1000 ml. blood were transfused. The postoperative hemorrhage was 200 ml. The patient was treated with Dicumarol for 12 days before and 14 days after the second operation.

Case 7. This man, 61 years of age, had pulmonary tuberculosis. A pleuropneumonectomy was performed for a destroyed left lung. At the operation a total thrombosis of the left pulmonary artery was found, and Dicumarol was immediately administered. Thoracoplasty was performed during this therapy 11 days later. During the second operation 500 ml. blood were transfused. The amount of fluid from the pleural drain after thoracoplasty (1800 ml.) was above normal but the amount of hemorrhage due to the last operation was difficult to evaluate because of the preceding pleuropneumonectomy and a complicating empyema. The patient was treated with Dicumarol for 10 days before and 16 days after operation.

Case 8. This patient, a man 58 years of age, suffered from tuberculosis and thrombophlebitis of the left arm. During extrapleural pneumonolysis 1500 ml. blood were transfused (normal 1000 ml.), but the bleeding did not appear to be more than normal. His postoperative condition was very bad, there being intense cyanosis and dyspnea and latent shock. A markedly decreased tolerance to Dicumarol entailed a low proconvertin-prothrombin level postoperatively (5 per cent) and the postoperative hemorrhage was 1400 ml. (normal 700). On the seventh postoperative day 1000 ml. blood were transfused. His condition promptly improved and the course of recovery was uneventful. The patient was treated with Dicumarol for three days before and nine days after operation.

Case 9. This female patient, 58 years of age, had sarcoidosis of the lungs, degenerative heart disease, previous postoperative thrombophlebitis, and marked obesity. Exploratory laparotomy for a suspected carcinoma of the stomach was performed, but normal conditions were found. The blood loss was completely normal. The patient was treated with Dicumarol for 5 days before and 12 days after operation.

Case 10. This man, aged 65, suffered from cancer of the lung, arteriosclerosis, dilated aorta and myocardial degeneration. During exploratory thoracotomy 1000 ml. blood were transfused. The postoperative hemorrhage was 280 ml. The patient was treated with Dicumarol for six days before and 19 days after operation.

Case 11. This patient was a woman, aged 37, with pulmonary tuberculosis. She was also three months pregnant and gave a history of several previous prolonged episodes of thrombophlebitis. Uterine curettage (therapeutic abortion) was performed. The blood loss was normal during and after the operation and no transfusions were given. The patient was treated with Dicumarol for eight days before and 14 days after operation.

Summary. Surgical operations were performed on these patients at proconvertin-prothrombin levels varying from 12 to 36 per cent. During operation, blood loss was not excessive in any case, though hemorrhage was above normal in the patient whose pulmonary artery was accidentally torn. After operation hemorrhage was very small in two cases, normal in most cases and slightly above normal average in two cases. In one of these two patients the hemorrhage was difficult to evaluate because of a preceding pleuropneumonectomy and a complicating empyema; in the other the proconvertin-prothrombin level was rather low postoperatively. In no case did excessive hemorrhage occur.

Discussion

The prophylactic effect of Dicumarol and similar agents against thrombosis and embolism has been especially striking in cardiovascular diseases with a high incidence of thromboembolic complications.[1, 16, 21] In Dicumarol therapy following surgery the evidence for a beneficial effect is less convincing.

In some series the incidence of thromboembolic episodes has been significantly reduced[3, 22] but in other series with carefully composed control groups the reduction is relatively small.[4, 5, 6, 23] The reason may be (1) that the treatment has been partly ineffective because of lack of reliable methods of control or (2) that the treatment has become effective too late after the operation.

In surgery a vast number of vessels are injured and large amounts of tissue thromboplastin enter the blood stream. At the same time local and general circulatory disturbances are inevitable. The peak of incidence of fatal pulmonary embolisms was found by Evoi[2] to occur on the seventh day after operation; 25 per cent of the total number of deaths had occurred by the fourth day, and 60 per cent by the seventh day after operation. Consequently postoperative thromboses are probably initiated before and during the surgical intervention. Allen[3] found that early thromboses should be treated by anticoagulant therapy within 24 hours to avoid embolism. Generally, postoperative anticoagulant treatment has been instituted on the first, second, or third day after operation; and relatively small initial doses have been used. Consequently the prothrombin-proconvertin concentration may not reach an effective level until four to seven days after operation. Administration of large doses of Dicumarol (or related compounds) after operations in order to obtain an early effective anticoagulant effect will produce unpredictable and often dangerous responses because of the postoperative decreased tolerance to Dicumarol.

It may be concluded, therefore, that an effective and controlled prophylaxis against thromboembolism in surgery can be obtained with Dicumarol only when the treatment is begun prior to and maintained during and after the operation. Obviously, uncontrollable hemorrhage is the main risk of this procedure. The spontaneously occurring hemorrhage during Dicumarol therapy has generally been slight, but not infrequently serious, and in a number of cases fatal bleeding has developed.[24] It is probable, however, that most instances of major hemorrhage have been caused by excessive doses of Dicumarol administered with inadequate methods of control.[1] This view is strongly supported by the very few instances of slight hemorrhage in long-term treatment which is carefully controlled by reliable methods.[16, 25]

The incidence of hemorrhage in patients treated with Dicumarol after surgery[3, 4, 5] and after delivery[7] was not larger than in other groups of patients, and excess bleeding from the wounds was not noted. Uterine curettage, caesarian section, manual release of placenta,[8] vein transplantation (two cases), and transfixation of arteriovenous fistulas (two cases)[12] have been performed without abnormal bleeding in patients previously dicumarolized. However, in the patients just referred to the prothrombin times during operation were not stated. In two known instances an emergency appendectomy has been performed without complications during Dicumarol therapy on patients with prolonged prothrombin times.[9, 10] In experimental surgery on dogs,[11] complete hemostasis in open wounds of the spleen could be obtained at prothrombin levels above and somewhat below 10 per cent of the normal, while the hemorrhage was uncontrollable at lower levels. Consequently, uninterrupted Dicumarol treatment during surgery necessitates the use of a standardized, accurate, and sensitive method for the control of the therapy, meticulous care in the dosage of Dicumarol, and a close clinical control of the patients. The moderate coagulation defects which occur under these conditions can be corrected in a very short time by blood transfusions and intravenous administration of vitamin K_1.[18, 19]

All of our group of patients showed a strong predisposition to thromboembolic incidents. Six patients had cancer of the lung. In a large series of patients of this category 30 per cent died in the postoperative period, 18 per cent of these deaths were caused by pulmonary embolism, and 12 per cent by coronary occlusions.[26] We consider a thromboembolic risk of this magnitude to be considerably

greater than the risk of hemorrhage in properly administrated Dicumarol therapy maintained during surgery.

Summary

1. Anticoagulant therapy with Dicumarol was instituted before and maintained at an effective level during and after major surgical interventions in 11 patients with a marked predisposition to thromboembolism. No excessive hemorrhage and no unusual complications were encountered.

2. A marked transient decrease in the level of proconvertin-prothrombin in blood occurred generally after large operations.

3. A standardized and sensitive method for the control of the therapy, and experience and care in regulating the dosage of Dicumarol are indispensable for a safe performance of the procedure.

4. In this way an effective prophylaxis against postoperative thromboembolic complications can be provided.

Sumario Español

1. Terapia anticoagulante con Dicumarol se instituyó antes y se mantuvo a un nivel efectivo durante y después de intervenciones quirúrgicas mayores en 11 pacientes con marcada predisposición al tromboembolismo. No se encontraron hemorragias excesivas o complicaciones fuera de lo usual.

2. Un marcado transitorio decremento en el nivel de proconverti-protrombina en la sangre ocurrió generalmente luego de operaciones mayores.

3. Un método regularizado y sensitivo para el control de la terapia y experiencia y cuidado en la regulación de la dosificación del Dicoumarol son indispensables para poder ejecutar este procedimiento inocuamente.

4. De esta manera se puede proveer una profilaxis efectiva para las complicaciones tromboembólicas post-operatorias.

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Atrial Rupture of the Heart

Report of Case following Atrial Infarction and Summary of 79 Cases Collected from the Literature

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This paper reports a case of atrial rupture of the heart and reviews 79 other cases collected from the literature proven by autopsy. Incidence, etiology, pathologic physiology, diagnosis and possible treatment are discussed. Infarction of the atrial wall due to an obliterative endarteritis or thrombotic occlusion is the most common cause of spontaneous rupture of the atrium. With a high index of suspicion of atrial rupture in a patient with atrial infarction or cardiac tamponade, earlier diagnosis and surgical treatment may become possible.

ATRIAL rupture of the heart is a dramatic event which leads inevitably to death. This paper reports the only case of atrial rupture among 5,900 autopsies at the Albany Hospital and summarizes the pertinent literature on atrial rupture as to etiology, diagnosis, pathologic physiology, sex, age, and treatment. A total of 79 cases of atrial rupture has been collected from the literature, classified and studied. The present report brings the total number of recorded instances of rupture of the atrium up to 80.

The term "atrial rupture" denotes a complete, acquired defect of the wall of either atrium through which the blood may leak into the pericardial sac and produce a fatal pericardial tamponade. This condition, never yet known to be diagnosed ante mortem, and suspected only once in 80 cases,[20] is frequently confused with ventricular rupture.

Ventricular rupture occurs in 8 to 10 per cent of patients who develop myocardial infarction[4] with a high incidence among insane[40] and hypertensive patients.[22] Atrial rupture, by contrast, is a much rarer condition. In the 710 combined cases of spontaneous rupture of the heart reported by Krumbhaar and Crowell[42] and by Davenport,[18] atrial rupture occurred in 51 patients. The right atrium was involved in 38 patients and the left in 13. Bright and Beck,[11] in a review of 152 cases of traumatic heart rupture, found the right atrium damaged in 36 patients and the left in 30. One had a perforation of the interatrial septum. Since Bright and Beck's review in 1935, only sporadic cases of atrial rupture have been reported.

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Case Report

J. H., AH 74724, a 64 year old white woman, was admitted to the Medical Service of the Albany Hospital on Sept. 9, 1940. She complained of weakness, vomiting, and lancinating precordial pain of one hour's duration. For the two preceding years, the patient had suffered from angina pectoris and dyspnea during exertion. One year prior to admission, she had chest pains attributed to pleurisy. Previous operations included oophorectomy, renal lithotomy, appendectomy, cholecystectomy, and herniorrhaphy.

On physical examination, the patient was conscious but appeared rather ill, and was evidently suffering severe precordial pain. She vomited occasionally. The blood pressure was 80/60; the pulse rate was 80; the heart sounds were distant and weak and the heart's action slightly irregular. No murmur or friction rub was audible.

Urinalysis showed 2 plus albumin and some leukocytes. The erythrocyte count was 4,800,000; the leukocyte count 13,800 per cubic millimeter, with 80 per cent polymorphonuclear cells and 20 per cent lymphocytes. The Wassermann test was negative. The blood nonprotein nitrogen was 45.4 mg. per 100 cc.

The patient's temperature, elevated to 101 F. on the second hospital day, returned to normal by the sixth hospital day. Her blood pressure rose to 120/80 within the first 24 hours. On the fourth hospital day, her pulse rate suddenly increased to 240 per minute and an electrocardiogram revealed paroxysmal auricular fibrillation (fig. 1). Sinus rhythm returned rather promptly after the administration of 0.3 Gm. of quinidine. Electrocardiograms before and after this episode showed regular sinus rhythm. The patient improved until the thirty-fifth hospital

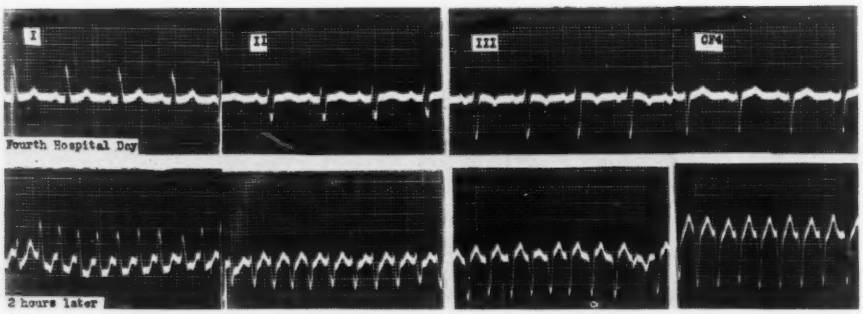

FIG. 1. Upper electrocardiogram taken on fourth hospital day shows normal sinus rhythm. The lower tracing taken two hours later shows the development of rapid paroxysmal atrial fibrillation.

day when she complained again of precordial pain. The temperature rose to 101 F. The blood pressure dropped to 90/70; the heart rhythm alternated between paroxysmal auricular fibrillation and regular sinus rhythm despite the administration of digitalis and quinidine. The severe chest pain persisted for several days. Shortly after awakening on the forty-first hospital day, the patient asked to be raised in bed. Before this could be done, she suddenly died.

The clinical diagnoses recorded ante mortem were recent and remote infarction of the left ventricle.

Postmortem Examination. An autopsy revealed an almost imperceptible perforation on the anterior surface of the right atrium near the coronary sinus which had resulted in a hemopericardium, consisting of 500 cc. of clotted blood and 200 cc. of serous fluid. The heart weighed 240 Gm. Calcified pulmonary valves and fusion of two aortic cusps with calcifications were noted. The walls of the coronary arteries were thickened but no occlusion was found.

Incidental findings included atherosclerosis of the aorta, generalized arteriosclerosis, acute congestion of the spleen and kidneys, and a large cyst in the right lobe of the liver.

Microscopically, the heart revealed evidence of old pericarditis with necrosis of some myocardial fibers in the region of the atrial rupture. The main coronary vessels with intact intima were patent. Some endarteritis was present. The small coronary branches showed lymphocytic cuffing, splitting of the muscle layer, desquamation of endothelial cells, and partial occlusion of the lumina by granulation tissue.

Pathologic diagnoses: (1) infarction of the right atrium, anterior wall, with softening, rupture and hemopericardium; (2) pericarditis, old, without scar tissue formation; (3) endarteritis of coronary vessels with narrowing of smaller branches; (4) congestion of spleen, kidneys and liver; (5) atherosclerosis of aorta; (6) valvulitis, aortic, atherosclerotic, old, with calcification; (7) cysts of right lobe of liver, and (8) generalized arteriosclerosis.

DISCUSSION

Review of Literature

Few of the reported cases contain adequate microscopic descriptions of the pathologic findings, and complete clinical data are often lacking. Electrocardiographic tracings are rarely published since many of the cases were recorded before the introduction of the electrocardiograph some two decades ago.

Rutherfoord recorded the first case of atrial rupture in 1828.[73] His patient, a 24 year old female, subject to "deep mental inquietude," had occasionally suffered from palpitation of the heart for about four years prior to her death.

Complaining of pains in the chest, she was bled by leeches and blood letting. After 22 ounces of blood were removed, "She did not show the slightest disposition to faint after the bleeding, but on lying down she suddenly exclaimed 'Oh dear, my heart! it will certainly burst: my feet feel so strange, they are quite dead: pray, put your hand on my heart, sir, it will come out.' I went immediately round to her bedside when she expired in my arms in a state similar to fainting." Autopsy demonstrated a rupture of the right atrium near the superior vena cava.

Subsequently, sporadic reports of atrial rupture have appeared in the world literature. Table 1* classifies these according to etiology.

* At the request of the Editor, table 1 is being omitted. In this table all reported cases of atrial rupture are summarized and classified as to etiology. Table 1 will be furnished on request.

Etiology of Atrial Rupture

Atrial rupture is almost always associated with or preceded by one of the following conditions: trauma, atrial infarction, fatty degeneration of the muscle, valvular heart disease, tumor of the heart or aneurysm of the atrium (table 1*). Several cases, whose etiology cannot be ascertained because of inadequate description, are listed under the heading of "miscellaneous." Trauma is the prime cause of atrial rupture. Atrial infarction is next.

A. *Atrial infarction* (10 cases. table 1, cases 1 to 10 inclusive*). It has been observed[17] that atrial infarction per se does not necessarily lead to atrial rupture. In fact, most patients do not develop atrial rupture after atrial infarction. However, in the collected series of 10 cases, which does include our own, atrial infarction actually preceded atrial rupture in every instance (table 1, cases 1 to 10).* In two of these patients, there was an associated infarction of the left ventricle. In the other eight cases, atrial infarction occurred without ventricular infarction.

In the 10 cases under discussion, the right atrium was involved more frequently than the left. Rupture of the right atrium occurred in seven; rupture of the left atrium, in three. The rupture was usually a single one, multiple ruptures being found in the same atrium in only one instance.

Atrial infarction may occur without thrombosis of a major artery. Hyaline changes and narrowing of the smaller coronary vessels without thrombosis produced the infarction in our case. In Cushing's series of atrial infarctions without rupture, only 1 of 31 cases demonstrated a gross occlusion of a coronary artery.[17] The gross recognition of atrial infarction may be difficult. In questionable cases, many tissue blocks must be taken for microscopic examination. Atrial thrombi, when present, often serve to call attention to the possibility of underlying atrial infarction.[76]

Before the work of Cushing and his associates[17] in 1942, the true incidence of atrial infarction was not realized. In 182 patients dying of myocardial infarction of the ventricle, these authors carefully searched for evidence of infarction in the auricles and found it present in 31 or 17 per cent. Söderström,[76] in 1948, independently confirmed and extended the preceding studies of Cushing in a most comprehensive and classic monograph. The material studied comprised 192 autopsy cases with mural thrombi in the cardiac atria. Atrial infarcts were practically impossible to recognize with the naked eye. Realization of the value of mural atrial thrombosis as an indicator led to the discovery of an increased number of underlying atrial infarctions, but only a fraction of mural thromboses yielded infarcts. Forty-seven examples of true infarcts were found with minor atrial lesions in 33 other cases. Clinical signs referable to atrial infarcts proved to be few and of little practical import. Electrocardiographic changes were not considered reliable indexes of infarction. There were no instances of atrial rupture, secondary to infarction, in either Cushing's or Söderström's series.

B. *"Fatty degeneration of the heart"* (7 cases. table 1, cases 11 to 17 inclusive*). Fatty degeneration and brown atrophy of the heart muscle are descriptive terms applied to cases of atrial rupture reported many years ago which, today, would be classified as infarction. Quain, for example, as early as 1850 pointed out that many instances of fatty degeneration and brown atrophy also manifested disease of the nutrient arteries.[65]

For most of their cases, the older authors gave as the cause of rupture either fatty degeneration of the heart or myocarditis. They contented themselves with the examination of the heart muscle only. In the second half of the nineteenth century, attention was focussed on the atheromatous changes in the coronary arteries. From that time on, an increasing number of observers indicated that the softening of the heart muscle was in the large majority of cases due to disease of the nutrient arteries of the heart.

Askey and Edwardes state that it has not been established whether fatty changes are greater than normal in the heart which has been ruptured.[5] Before ischemic necrosis resulting from coronary occlusion was recognized,

* See foot note page 222.

the myomalacia was usually ascribed to fatty degeneration. When the true nature of the necrosis was realized, fatty changes were generally rejected by pathologists as having little if any etiologic significance. This same attitude applied not only to fatty degeneration but to fatty infiltration as well. It is now a fairly well accepted fact that fatty degeneration occurs no more frequently in the hearts of myocardial infarction than in the hearts of apparently normal persons. Beresford and Earl[9a] suggest that increased fatty infiltration may be a factor in inducing rupture. It is argued that ischemia produces necrosis of fat with extreme softening, almost to the point of liquefaction. The softened intramural fat, it is thus believed, facilitates the extension of a tear through the cardiac wall and hemorrhage, once initiated, forces its way into the epicardium.

It is rather significant that no case of atrial rupture has been ascribed to fatty degeneration since 1905, which fact offers convincing proof of a decided change in our concept as to the mechanism of cardiac rupture.

C. *Trauma* (19 cases. table 1, cases 18 to 36 inclusive*). Various types of trauma may lead to rupture of any of the heart chambers. In this review, the nonpenetrating type of trauma leading to atrial rupture is the sole variety of injury considered. Only a single chamber is, as a rule, involved. Most cases of atrial rupture have been produced by direct blows to the chest, but several instances have been reported which were associated with trauma to the head, leg or abdomen only.

Three theories have been advanced to explain the production mechanisms of atrial rupture by nonpenetrating trauma.[11] In the first mechanism, direct compression of the heart between the sternum and the dorsal vertebrae is believed to be capable of producing atrial rupture. This is the most plausible explanation in patients who die from atrial rupture immediately after an accident.

In the second mechanism, contusion of the heart with subsequent necrosis of the injured myocardium is thought to lead to rupture of the atrium. An example of this type is that of a 9 year old boy (case 23) who died suddenly seven days after being assaulted by a group of boys. Autopsy demonstrated a slit in the left atrium and a clot in the pericardial sac of several days duration. Similarly, a five year old girl (case 25) fell two feet from a porch without evidence of injury being found. Seven days later, she died in her sleep. Autopsy showed rupture of the left atrium.

In the third and less clearly established mechanism, trauma to the head, leg, or abdomen appears to have led in some instances to atrial rupture, by increasing the intracardiac pressure. Cases 19 and 34 are good examples of this. Experimental support for this concept is furnished by the work of Bright and Beck.[11] They tried to produce cardiac rupture in dogs by indirect trauma applied to the legs and abdomens of the animals, and found that the right atrial pressure rose in their animals. They were also able to produce cardiac dilatation and heart failure together with small epicardial and myocardial hemorrhages, but no actual rupture of the heart occurred in their dogs.

The condition of the myocardium at the time of injury definitely influences the production of atrial rupture by nonpenetrating injury. Atrial rupture is more likely to occur when trauma is inflicted upon a previously damaged myocardium.

D. *Valvular heart disease* (5 cases, presumably all chronic rheumatic heart disease. table 1, cases 37 to 41 inclusive*). Five cases of atrial rupture associated with valvular heart disease have been reported. Four had involvement of both mitral and aortic valves; the fifth case (case 41) showed only mitral stenosis. The right atrium was involved in four instances; the left, in one. Two of these cases (cases 39 and 40) also had subacute bacterial endocarditis which may have caused additional damage to the myocardium.

In this group, it seems reasonable to believe that elevated atrial pressures produced by the valvular lesions contributed to the rupture and that the myocardium, already weakened by disease, gave way to the strain of the elevated atrial pressure. In one patient (case 41),

* See foot note page 222.

pulmonary emboli also may well have contributed to an elevated pressure in the right atrium.

E. *Tumors* (3 cases. table 1, cases 42 to 44 inclusive*). Tumors were associated with rupture of the left atrium in three instances. One patient had a primary rhabdomyosarcoma of the heart; the second, a metastatic lesion to the heart from carcinoma of the duodenum; and the third, infiltration of the myocardium by leukemic cells of the myeloid type.

F. *Aneurysm of Atrium* (3 cases. table 1, cases 45 to 47 inclusive*). Three cases of atrial rupture associated with aneurysm of the atrial wall were reported between 1903 and 1908.

G. *Miscellaneous* (33 cases, table 1, cases 48 to 80 inclusive*). This category includes 33 atrial ruptures of uncertain etiology which cannot be classified because of incompletely recorded information. Three patients had coronary artery disease without infarction of the atrium. In the first patient (case 77), the unusual exertion of cranking a Diesel engine produced atrial rupture despite apparent good health. After working for an hour, he complained of something "going wrong" in his stomach and died suddenly. Autopsy revealed multiple ruptures of the right atrium without necrosis in the region of the ruptures. The right coronary artery contained multiple foci of medial necrosis with calcification, atheroma formation, intimal thickening, and splitting of the elastica.

In the second patient (case 66), a 26 year old man with acute nephritis, atrial rupture was attributed to "degeneration of the heart" from Bright's disease. Atheromatous changes of the atria and of the aorta were present.

The third patient (case 75), a 55 year old woman, died suddenly in a mental institution. Autopsy revealed atherosclerosis of the coronary arteries and rupture of the right atrium.

Unusual exertion is not a common antecedent of atrial rupture. In only four cases was unusual exertion mentioned, such as rowing a boat, cranking a Diesel engine, drawing a truck, and carrying a weight of 20 pounds. One patient was stricken while straining at stool and one, while attempting to vomit.

Several patients with syphilis also developed atrial rupture but there is insufficient evidence to implicate syphilis as an etiologic factor.

Diagnosis of Atrial Rupture

There is no instance of atrial rupture diagnosed ante mortem in the 80 cases comprising this study. Di Ilesi and associates[20] suspected it and came nearer to making an actual ante mortem diagnosis in 1949 than anyone. A 69 year old white man, "suffered an acute myocardial infarction involving the posterior wall of the left ventricle, right auricle and interventricular septum. The elevation of the P-Ta segment in leads II and III offered a clue to the presence of a recent infarction involving the posterior wall of one of the auricles." The development of symptoms and signs varies with the length of the survival time of the patient. Symptoms, in general, closely resemble those of myocardial infarction of the ventricle. Severe excruciating chest pain, often radiating to the back, is the commonest complaint of patients who survive the initial episode. Weakness, dyspnea and, occasionally, syncope from a fall in blood pressure are prone to occur.

Patients surviving the atrial rupture for a number of hours or days may develop such signs of cardiac tamponade as a small weak pulse, distant heart sounds, an increased area of cardiac dullness, and distended neck veins. Cardiac arrhythmias are common. Although there are no characteristic auscultatory findings, in patient 65 a splashing sound was audible during systole. In patient 53, the examiner heard a rushing sound at the presumptive time of rupture and a previously audible bruit disappeared. Because of the paucity of characteristic diagnostic physical signs recorded in such cases, it is of interest to quote briefly a portion of the author's original description of the findings on auscultation in one of these two instances where an unusual bruit was heard.

Case 65, reported by H. B. Smith in 1881, deals with a 37 year old man first seen in April 1881 with pain in the region of the heart. A

* See foot note page 222.

constant ache had been present for the preceding six months. Examination was negative. Several months later, while stooping over after having built a fire, he fell unconscious to the floor. Examined 20 minutes later, he was found to be conscious, breathing hurriedly and deeply, with a terrified expression of countenance, writhing and tossing in his bed, calling to be raised up one minute and turned over the next, asking to be rubbed on the extremities, back and chest, while great drops of sweat stood in his face. He asked frequently for water; the stomach seemed distended with gas. "I was able to make but a very slight examination because of his writhing and tossing about. He was pulseless at the wrist and the extremities were cold to the knees and elbows. On placing my ear to the precordia, I could faintly hear a muffled splashing sound of the heart, during the systole only. I could hear no second sound." No pain was present, only a sense of smothering. Death occurred one and a quarter hours after the attack. Postmortem examination showed pericardium filled to bursting with blood. There was a three fourths inch jagged rupture in the wall of the left atrium.

In estimating the survival period after atrial rupture, one is handicapped by difficulty in differentiating the symptoms of the underlying condition from those of actual rupture. Nevertheless, pathologic evidence such as pericardial reaction, and organization of the pericardial clot, indicate that some patients with atrial rupture have survived up to nine weeks. This condition, however, is always fatal, with 61 per cent of the patients dying instantaneously after the rupture.

Barnes[6] states that atrial rupture usually leads to more rapid death than does ventricular rupture, since extravasation occurs more frequently in the former condition. Our data, however, indicate that death is less rapid after atrial rupture than after ventricular rupture, since 15 per cent of patients with atrial rupture have survived over 24 hours. In ventricular rupture, less than 2 per cent of patients live 24 hours.[14] Cases of traumatic atrial rupture usually have the longest survival period. The case reported by Rixford (case 36), is a striking example of this; the patient was kicked in the chest by a cow and survived nine weeks. During this period, three pericardial taps yielded two quarts of old blood.

The electrocardiogram may aid in the diagnosis of atrial rupture by indicating atrial infarction prior to the rupture and pericarditis after the rupture. In a series of 31 patients with atrial infarctions without rupture, Cushing and co-workers[17] noted atrial extrasystoles, atrial fibrillation, wandering pacemaker, and nodal rhythm in 23 who were subjected to electrocardiographic study. Occasionally, they found depression of the P-Q segment. Similar arrhythmias, except for atrial fibrillation, occurred in experimental infarction of the atrium in dogs. In Söderström's series of 47 cases of atrial infarction,[76] atrial fibrillation developed in one-third of the patients with regular sinus rhythm prior to the infarction. Rapid auricular fibrillation also was recorded in the electrocardiogram of our patient (fig. 1).

Although elevated or depressed PTa segments, especially in leads II and III, are diagnostic of atrial infarction, these changes are difficult to see unless complete heart block is present.[1, 28, 45, 46] Depression of the P-Ta segment in leads II and III indicates infarction of the anterolateral portion of the right atrium. It occurs more frequently than P-Ta elevation, which indicates involvement of the posterior wall of the atria.[32] Söderström[76] suggests that an abnormally short P-R (in the absence of a Wolff-Parkinson-White syndrome) with upright P waves may be a sign of infarction of the right atrium.

The electrocardiographic pattern of pericarditis may occur after atrial rupture because of blood in the pericardial sac. Randles, Gorham and Dresbach[66] described S-T segment elevation in all limb leads of dogs in which atrial rupture was produced experimentally. This pattern was undoubtedly the result of pericarditis. Similar S-T elevations occurred in the electrocardiogram of the patient with atrial rupture reported by Clowe, Kellert, and Gorham.[14]

A roentgenogram of the heart after atrial

rupture may indicate pericardial effusion by an enlarged heart shadow. Aspiration of blood from the pericardial sac will also confirm the diagnosis of cardiac tamponade.

Pathologic Physiology of Atrial Rupture

Two theories have been advanced to explain the production of atrial rupture.[4] The first assumes that an increased intra-atrial pressure leads to a bursting of the wall of the chamber. The second postulates a direct tearing of diseased atrial musculature by the force of its own contraction. Probably a combination of both factors is involved in atrial rupture. In patients with atrial fibrillation who develop atrial rupture, the increased intracavity pressure is perhaps more important than the muscular contraction factor, although Prinzmetal and his co-workers[63] have demonstrated small muscular contractions in fibrillating atria.

Variations in the anatomy and intraluminal pressure of the atria may influence the development of atrial rupture. Söderström[76] points out that the endocardium of the trabeculated portion of the right atrium is extremely thin, consisting merely of endothelium in contact with perimysial connective tissue of the myocardium. In the smooth-walled parts of the atria, the myocardium normally varies from 1 to 3 mm. in thickness. Some portions of the right atrium actually lack myocardial tissue between endocardium and pericardium. The fact that the right atrium is generally thinner and less muscular than the left probably accounts for the increased incidence of rupture in the right atrium.[89]

Although the atrial blood supply exhibits considerable anatomic variations, branches of the right coronary artery arising near its origin customarily nourish the wall of the right atrium. Branches of the left circumflex artery supply the left atrial wall.[78] In addition, extracoronary anastomoses are present between the atria and the vasae vasorum of the venae cavae and the pulmonary veins.[76] It has also been suggested that the atria may obtain nutrition directly from their lumina.

Cushing and associates[17] ascribe the higher incidence of right atrial infarction to the lower oxygen content of the blood in the right atrium. A second but more important fact is that thrombosis of the right coronary artery usually occurs in the proximal 2 or 3 cm. which also occludes the branches supplying the right atrium. This is more likely the reason for the higher incidence of right atrial rupture than a difference in the oxygen content of blood in the two atria.

An increase in the intraluminal pressure also appears significant in any rupture of the heart. The lower incidence of atrial rupture, as compared with ventricular rupture, seems closely related to the much lower intraluminal pressure of the atria which, in the right atrium, varies from -2 to $+2$ mm. Hg and, in the left atrium, is only slightly higher.[7, 10, 60] Considerably higher atrial pressures may be encountered in patients with pulmonary disease or valvular heart disease, especially if they have congestive heart failure or atrial fibrillation.[7, 10]

In the presence of lower atrial pressures, some ruptures may be accompanied by "slow leaks" which may, occasionally, even seal off with a clot. Examples of this are to be found especially among traumatic cases: Case 23, 7 days; case 25, 7 days; case 34, 12 days and case 36, 9 weeks. In experimental atrial rupture produced in dogs, it has been clearly shown that clot formation and healing are so rapid that a saw-string suture is necessary to insure bleeding after 24 hours.[66] On the other hand, all five instances of atrial rupture recorded in patients with valvular heart disease (and, presumably higher atrial pressures) ended in sudden death.

Several attempts have been made to calculate mathematically the pressures influencing rupture.[26, 27, 67, 94] These studies suffer from oversimplification, since this proves to be a highly complex problem with many interdependent variables.

Sex and Age Factors

Atrial rupture, in contrast to ventricular rupture, occurs about twice as frequently among males as females in almost all groups listed in table 2; 68.6 per cent of patients with

TABLE 2.—*Incidence of Atrial Rupture According to Sex*

Sex	Infarct	"Fatty Degeneration"*	Trauma	Valvular	Tumor	Aneurysm	†Others	Total	%
Male	7	5	17	4	1	2	12	48	68.6
Female	3	2	2	1	2	1	11	22	31.4
Totals	10	7	19	5	3	3	23	70	100.0

* May be considered as infarct. † 10 cases recorded without notation as to age.

TABLE 3.—*Incidence of Atrial Rupture According to Age*

	Infarct	"Fatty Degeneration"*	Trauma	Valvular	Tumor	Aneurysm	Others	Total	%
Over 70	—	—	1	—	—	—	1	2	3.3
60–69	6	4	—	—	—	1	2	13	21.7
50–59	2	—	—	2	—	—	2	6	10.0
40–49	1	1	5	—	—	1	3	11	18.3
30–39	—	2	4	3	—	—	5	14	23.4
20–29	—	—	2	—	1	1	5	9	15.0
Under 20	1	—	3	—	1	—	—	5	8.3
Totals	10	7	15	5	2	3	18	60†	100.0

* May be considered as infarct. † 20 cases with inadequate data reported.

atrial rupture were males and 31.4 per cent were females. On the other hand, Oblath and coworkers found 58.75 per cent of their 80 patients with ventricular rupture were women and only 41.25 per cent were men.[58a]

It is also of interest that the collected series of 17 atrial ruptures following atrial infarction includes five patients below the age of 50 while no patient was below 50 years of age in the series of ventricular ruptures reported by Oblath and colleagues.[58a] The reasons for the sex and age differences between atrial and ventricular ruptures are not readily explained. The small numbers involved may not be statistically significant.

Tables 2 and 3 are necessarily incomplete because of inadequate reporting of the earlier cases in the literature.

Treatment

No treatment of atrial rupture has been of avail. With the advent of modern cardiac surgery, repair of the atrial rupture becomes feasible if the diagnosis is made in time and the leak is a slow one.[11] A high index of suspicion of atrial rupture in a patient with atrial infarction or cardiac tamponade may conceivably some day lead to an earlier diagnosis and possible surgical treatment. Aspiration of blood from the pericardial sac to relieve cardiac tamponade is of little value unless surgical repair follows.

SUMMARY

1. An additional case of atrial rupture in a 64 year old woman is reported.

2. Seventy-nine cases of atrial rupture have been collected, classified and studied, making a total of 80, up to Jan. 1, 1953.

3. Atrial infarction and trauma are the chief causes of atrial rupture, accounting for 17 and 19 cases, respectively.

4. Obliterative endarteritis of the atrial branches of the coronary arteries rather than thrombotic occlusion is often the inciting factor of atrial infarction and will be found more often if sought for at autopsy.

5. In contrast to ventricular rupture, atrial rupture occurs more frequently in men than in women. Although sudden death is the rule, survival up to nine weeks has been observed. Contrary to a previously published

report, death from ventricular rupture occurs more quickly than from atrial rupture. Unusual exertion does not commonly precede atrial rupture.

6. The diagnostic features and pathologic physiology of atrial rupture are discussed.

7. No case of atrial rupture in which the correct diagnosis was made ante mortem has thus far been recorded. Electrocardiographic changes occasionally occur which should arouse suspicion of this diagnosis. Only one instance of such suspicion was found in the literature.

8. A high index of suspicion of atrial rupture in a patient with atrial infarction or cardiac tamponade may conceivably some day lead to an earlier diagnosis and possible surgical treatment.

Sumario Español

1. Un caso adicional de rotura atrial en una mujer de 64 años de edad se informa.

2. Setenta y nueve casos de rotura atrial han sido coleccionados, clasificados y estudiados, haciendo un total de 80, hasta enero 1°, 1953.

3. Infarto atrial y trauma son las causas de rotura atrial más importantes, ocasionando de 17 a 19 casos respectivamente.

4. Endarteritis obliterante de las ramas atriales de las arterias coronarias más bien que oclusión trombótica es frecuentemente el factor incitante de infarto atrial y se encontrará más frecuentemente si se piensa en ello durante la autopsia.

5. En contraste con rotura ventricular, rotura atrial ocurre más frecuentemente en la mujer que en el hombre. Aunque muerte repentina es la regla, supervivencia hasta nueve semanas ha sido observada. Contrario a informes previamente publicados, la muerte causada por rotura ventricular ocurre más prontamente que la ocasionada por rotura atrial. Ejercicio extraordinario no precede comunmente la rotura atrial.

6. Los distintivos diagnósticos y fisiología patológica de la rotura atrial se discuten.

7. Ningún caso de rotura atrial en el cual el diagnóstico correcto se halla hecho ante mortem ha sido aún informado. Cambios electrocardiográficos ocasionalmente ocurren que debieran despertar la sospecha de este diagnóstico. Solamente un caso de tal sospecha se encontró en la literatura.

8. Un índice alto de sospecha de rotura atrial en un paciente con infarto atrial o taponamiento puede que haga posible algún día el diagnóstico temprano y se pueda intervenir quirurgicamente.

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Persistent Supraventricular Tachycardia

Case Report with Review of Literature

By Norman Shachnow, M.D., Stanley Spellman, M.D., and Ira Rubin, M.D.

A summary of all reported cases of persistent supraventricular tachycardia, as contrasted with paroxysmal and repetitive tachycardia, is presented, along with an additional well-documented instance covering an 11-year period. The distinctive features of persistent tachycardia are included.

ONLY 13 cases of persistent supraventricular tachycardia have been reported in the available medical literature, and few of these have had prolonged follow-up study.[1-9] Unlike paroxysmal tachycardia, persistent supraventricular tachycardia occurs rarely and is characteristically refractory to treatment. We wish to present an additional and well-documented case report of persistent auricular tachycardia of 11 years' duration in a 15 year old boy which has remained refractory to treatment, and to focus attention on the pertinent features of this type of obstinate arrhythmia. A summary of all the reported cases of established persistent supraventricular tachycardia is included (table 1).* Only those instances of continuous tachycardia of at least two months duration have been considered.

Case Report

A 14 year old white boy was admitted to Montefiore Hospital on March 24, 1952 (case no. 57407). Details of the mother's pregnancy and delivery were in no way unusual. The child was not cyanotic or dyspneic at birth and no murmurs or arrhythmia were noted. Development was normal. At the age of 6 months a "somewhat harsh systolic murmur" over the entire heart was noted by the family physician, who made no mention then of an unusual cardiac rate. At 14 months, the boy was treated for bronchitis. There is no history of diphtheria, rheumatic fever, or scarlet fever. No other childhood illnesses are recorded.

The patient was admitted to another hospital on Nov. 2, 1942, with a history of sudden paralysis of the right side of his body, loss of speech and incontinence. Examination at that time revealed a well-nourished 4 year old boy with hemiplegia and aphasia. The heart rate was rapid. No murmurs were audible. The remainder of the examination was negative. Laboratory data were normal. No evidence of cardiac enlargement was demonstrated on roentgenographic examination. The initial electrocardiogram revealed a supraventricular tachycardia with 1:1 conduction at a rate of 270 per minute (fig. 1, 11-20-42). On the same day the rhythm reverted to a regular sinus tachycardia (fig. 1). This proved to be a transient change, for during the remainder of the hospitalization, an auricular tachycardia was present with a varying auricular rate up to 290 per minute, and a ventricular response ranging from 45 per minute to 290 per minute (fig. 1). Various maneuvers for breaking the arrhythmia, including carotid sinus and eyeball pressure, and therapeutic trials of quinidine and digitalis failed to alter the basic rhythm, though digitalis caused changes in the degree of block. It will be noted, however, that the single tracing obtained on Nov. 20, 1942 (fig. 1), revealed an apparent transient sinus tachycardia, which did not recur. The ventricular rate was reasonably well controlled, and no evidence of congestive heart failure appeared. Speech gradually returned and the patient recovered almost complete use of his right leg but only partial motion of his right arm.

Following discharge on March 3, 1943, the patient was referred to a convalescent home. On June 1, 1943, he developed signs of congestive heart failure with distended neck veins and an enlarged liver, requiring rapid digitalization. Between 1943 and 1950, periodic examinations at a cardiac clinic revealed persistent auricular tachycardia with a varying ventricular rate, confirmed by serial electrocardiograms.

The patient first came to our attention on June 9, 1951, and has been followed periodically since then. Examination at that time revealed a rapid heart rate. He was admitted to Montefiore Hospital for further study on March 24, 1952. The patient stated he was conscious of changes in his heart rate, particularly when it became very rapid, but was otherwise asymptomatic. At these times he would

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* At the request of the Editor, the table summarizing these cases is being omitted, but will be furnished on request.

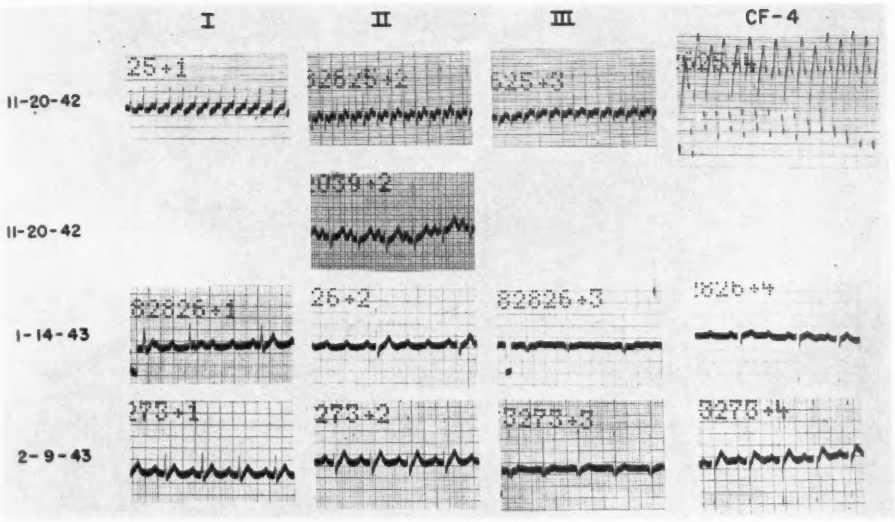

FIG. 1. Electrocardiogram of 11–20–42 reveals a 1:1 tachycardia. Tracing just below of the same date demonstrates the probable sinus tachycardia. (See text.) Tracing of 1–14–43 reveals auricular tachycardia with a varying degree of block. Tracing taken on 2–9–43 shows a tachycardia with a 2:1 block.

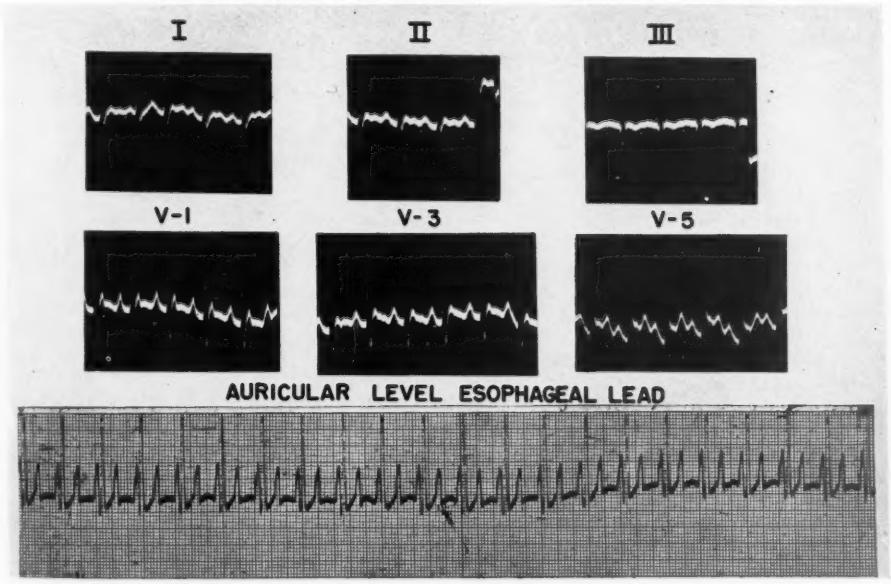

FIG. 2. Electrocardiogram of April 1952 reveals the persistent auricular tachycardia, with a 2:1 block clearly demonstrated by esophageal lead taken at the auricular level.

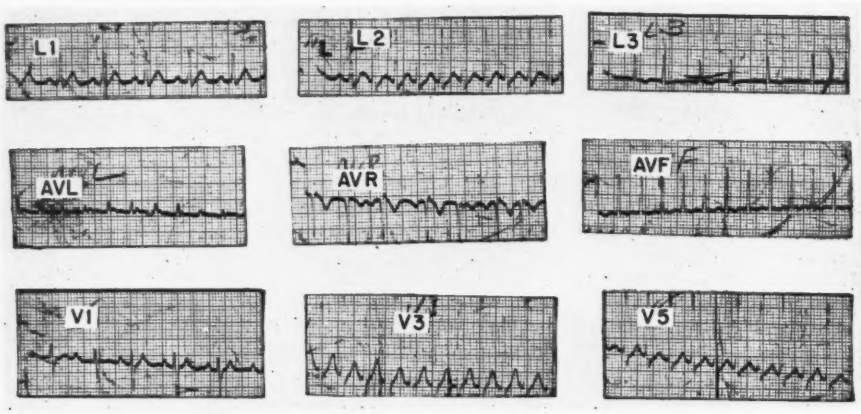

FIG. 3. Electrocardiogram of 10–23–53 shows auricular tachycardia with runs of 1:1 conduction, and electrical alternans best seen in lead II.

decrease his activity until the rate slowed. Physical examination revealed a well-developed, well-nourished, moderately obese white boy with a spastic paralysis of the right arm, weakness of the right leg, and abnormal reflexes compatible with a previous cerebrovascular accident. No murmurs were audible, and the heart was not enlarged either on fluoroscopy or roentgenography. Laboratory examinations, including venous pressure and circulation times, were within normal limits. Radioactive iodine uptake and urinary 17-ketosteroids were normal. Electrocardiograms revealed auricular tachycardia with a 2:1 block confirmed by esophageal leads (fig. 2). Quinidine, Digoxin and Prostigmine in the usual therapeutic doses did not alter the basic rhythm. The auricular rate varied between 200 and 300 beats per minute. The ventricular rate was usually 110 to 120 beats per minute at rest and increased to 150 beats per minute on exercise, but variation occurred as shown in figures 1 and 2. On one occasion the ventricular rate was observed to change from 240 to 120 per minute within a matter of seconds.

In May 1952, following discharge from the hospital, the digitalis dosage was reduced and then discontinued. In June 1952, his ventricular rate rose to between 200 and 240 beats per minute, and the boy complained of palpitations and slight dyspnea on exertion. Redigitalization slowed his ventricular rate and he became asymptomatic. In June 1953, an electrocardiogram revealed the persistent auricular tachycardia with 2:1 and occasionally 3:1 block. On Oct. 23, 1953, he again complained of palpitation and some dyspnea. An electrocardiogram revealed auricular tachycardia with runs of 1:1 conduction at a rate of 200 per minute, with electrical alternans (fig. 3). Without any treatment except sedation, and with no change in digitalis medication, the block increased to 2:1 and then 3:1, and the patient became again relatively asymptomatic. He is being maintained on digitalis.

DISCUSSION

The diagnosis of auricular tachycardia was established in this child at the age of 4 following a cerebrovascular accident. Whether this rhythm has been present since birth cannot be determined. Periodic electrocardiograms taken over the past 11 years reveal the persistently rapid auricular rate with varying degrees of heart block (fig. 1). The possible single exception was the tracing dated Nov. 20, 1942 (fig. 1), which reveals a reversion to an apparent sinus tachycardia. However, this tracing may also be interpreted as showing a slow auricular tachycardia, inasmuch as the P wave and the P-R interval are the same as those present in the other electrocardiograms. This episode was of short duration and has never recurred on any of the numerous subsequent tracings. The only evidence of the possible presence of a sinus rhythm was provided on that occasion.

The sudden onset of the hemiplegia in the absence of any other illness, and the normal development since then suggests that the arrhythmia with probable embolization was responsible for the cerebrovascular accident. The absence of cardiac enlargement or murmurs appears to rule out the usual etiologic forms of heart disease. There is no history of myocarditis, nor evidence of a demonstrable

ongenital defect. The auricular rate varies rom time to time, but always remains between 00 and 300 per minute. The etiology of this entirely unknown.

At the age of 4, signs of congestive heart ailure developed, which responded well to ntravenous digitalis. It is likely that a persistntly high ventricular rate was related to this pisode. The patient remained asymptomatic or many years thereafter, except for the awareess of changes in his heart rate.

In reviewing the literature for other established instances of persistent supraventricular tachycardia, of two months duration or more, only 13 other cases were found. We were careful to distinguish these cases from those with repetitive tachycardia. In this latter group evidence of normal sinus rhythm could be demonstrated repeatedly during the course of the tachycardia,[6, 10] whereas in the persistent type evidence of normal sinus rhythm could not be demonstrated for prolonged periods despite frequently repeated tracings.

Palpitation or awareness of the heartbeat was the most common symptom in the group, and was usually accompanied by slight shortness of breath, especially on exertion. However, five of the patients were asymptomatic, the arrhythmia having been discovered during examination for other reasons. The tachycardia first occurred before the age of 20 in 11 of the reported cases. There is no evidence that the arrhythmia was present at birth in any of the patients. One patient is said to have had tachycardia at 6 months of age,[8] while another patient was 34 years of age when his tachycardia first began.[9] The oldest patient of the group was first seen at the age of 59 because of a sacroiliac strain, but was otherwise asymptomatic although he was told of a tachycardia 43 years before.[2]

Cardiac enlargement was noted in only three instances,[5, 8, 9] and a murmur was described in only one case.[8] No evidence of possible etiologic factors, such as myocarditis or thyroid disease, was found in any of these patients.

Congestive heart failure occurred during the course of the arrhythmia in three of the patients, including our own, and was readily controlled by the usual measures in each instance. In the case cited by Claiborne, which most closely resembles our own, congestive heart failure occurred at the age of 4 and the patient required digitalis thereafter.[7] The other patient in whom congestive heart failure appeared was a 45 year old white man with a tachycardia which lasted 498 days.[9]

The auricular rate in our patient has always remained between 200 and 300 per minute. In the eight other instances where the auricular rate was specifically recorded, it usually varied between 120 and 200 per minute. A varying degree of A-V block was not unusual, with a ventricular rate usually between 120 and 180 per minute.

This group of patients was characteristically refractory to treatment. Sedation, vagal stimulation, quinidine, Pronestyl, digitalis and other measures failed to alter the basic rhythm. Digitalis was the most effective drug used, for it slowed the ventricular rate in the majority of instances in which it was employed, though usually it had no effect on the auricular mechanism. In three cases digitalis temporarily abolished the tachycardia.[4, 5, 8] In one of these patients, a 6 year old child, digitalis was ineffective in altering the rhythm when the child was 16 months of age but converted the tachycardia to regular sinus rhythm when the child was 6 years of age.[8]

Summary

A 15 year old boy with a persistent and refractory supraventricular tachycardia, well-documented over an 11-year period, is presented. The complications of hemiplegia and heart failure have appeared despite the absence clinically detectable organic heart disease. A review of all other cases with persistent auricular tachycardia of at least two months duration is included. Attention is drawn to some of the distinctive features of persistent tachycardia, in contrast with paroxysmal and repetitive tachycardia.

Sumario Español

Se informa el caso de un niño de 15 años con una taquicardia supraventricular refractoria y persistente, bien documentada por un período de 11 años. Las complicaciones de hemiplegia

y descompensación cardíaca han aparecido no obstante la ausencia clínica de enfermedad orgánica cardíaca. Un repaso de todos los otros casos con taquicardia auricular persistente de por lo menos dos meses de duración se incluye. Se llama la atención ha algunas de las características distintivas de la taquicardia persistente, en contraste con la taquicardia paroxística y repetitiva.

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Effects of Cortisone, Hydrocortisone and Corticotropin on Lipemia, Glycemia and Atherogenesis in Cholesterol-Fed Chicks

By JEREMIAH STAMLER, M.D., RUTH PICK, M.D. AND LOUIS N. KATZ, M.D.

Hydrocortisone markedly affected carbohydrate, protein, lipid and electrolyte metabolism of cholesterol-fed cockerels (intact, alloxanized and depancreatized). Despite steroid-induced diabetes and hyperadrenalism, associated with enhancement of hypercholesterolemic hyperlipemia, no hypertension or intensification of atherogenesis (aortic or coronary artery) supervened. Corticotropin (ACTH) produced similar effects. Cortisone was relatively inactive as a glycocorticoid in this avian species. Despite its apparently slight metabolic activity, however, it moderately elevated blood pressure and intensified atherogenesis.

HUMAN beings with hyperadrenocorticism (e.g. Cushing's syndrome) frequently develop premature, severe atherosclerosis.[7, 8] This fact assumes new importance at the present time, when chronic hyperadrenocortical states are being artificially induced on a large scale for therapeutic purposes. The widespread utilization of corticotropin (ACTH) and adrenal steroids in clinical medicine compels a thorough-going examination of their effects on atherogenesis. Towards this end, we previously studied the influences of desoxycorticosterone acetate (DCA) on avian experimental atherosclerosis.[9] The present investigation analyzed the effects of cortisone (compound E), hydrocortisone (compound F), and adrenocorticotropic hormone (ACTH)* on blood pressure, lipemia, glycemia, and aorta and coronary atherogenesis in cholesterol-fed cockerels. Further, these experiments were designed to study the influence of the diabetic state on lipid metabolism and atherogenesis in chicks. Sustained diabetes mellitus was induced for the first time in this avian species by a combination of alloxanization or pancreatectomy plus the glucocorticoid compound F.[8, 10-15]

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Some of these findings were presented at meetings of the American Society for the Study of Arteriosclerosis,[1-3] the Council for High Blood Pressure Research of the American Heart Association,[4] and the American Physiological Society.[5, 6]

This work was done during Dr. Stamler's tenure of a Fellowship as an Established Investigator of the American Heart Association.

* It is a pleasure to express our appreciation to Drs. R. Meyer and C. J. O'Donovan of the Armour Laboratories, and to Drs. E. Alpert and A. Gibson of Merck and Co., Inc. for generous supplies of ACTH and compound F, respectively.

METHODS

The experimental designs and technics were generally in accord with the standardized procedures of the department's atherosclerosis research group.[8] Altogether, five series of chronic experiments were completed, one with cortisone, two with hydrocortisone and two with corticotropin (ACTH), utilizing a total of 178 chicks (table 1). One day old Hyline cockerels were obtained from a commercial hatchery and reared in a battery brooder. They were maintained on a chick starter mash and tap water *ad lib.* prior to institution of the experimental regimens. In essence, these experimental regimens involved the study of pairs of intact cholesterol-fed cockerels, one group (control) of the pair receiving no hormone, the other (experimental) receiving parenteral hormone (table 1). Further, the experiments with compound F included pairs of alloxanized and depancreatized cockerels, in order to study cholesterol-induced experimental atherogenesis in insulin-deficient steroid-diabetic chicks. Two intravenous injections of alloxan (50 mg.) were given at intervals of one week, one or two weeks before institution of the experimental regimens. Pancreatectomy was similarly accomplished two to three weeks prior to beginning the study. Completeness of pancreatectomy was confirmed at autopsy.

A weekly record was kept of feed intake, weight and comb size of individual birds. Water intake data were also collected over several days during

TABLE 1.—*Experimental Regimens*

Series	Group No.	No. of Chicks	Chick Age During Experiment—weeks	Diet	Type Group	Hormone Dosage—‖ mg/chick/day
BC9	1	25	1–11*	0.5 C-O†	Intact control	0
BC9	2	25	1–11*	0.5 C-O	Intact cortisone	1–15‡
BC11	3	12	9–17	0.5 C-O	Intact control	0
BC11	4	12	9–17	0.5 C-O	Intact ACTH	6–8‡§
BC19	3	12	12–19	1.0 C-O†	Intact control	0
BC19	4	12	12–19	1.0 C-O	Intact ACTH	10–25‡¶
BC15	5	10	13–21	0.5 C-O	Intact control	0
BC15	6	10	13–21	0.5 C-O	Intact hydrocortisone	1–2‡
BC15	7	10	13–21	0.5 C-O	Alloxanized control	0
BC15	8	10	13–21	0.5 C-O	Alloxanized hydrocortisone	1–2‡
BC15	9	10	13–21	0.5 C-O	Pancreatectomized control	0
BC15	10	10	13–21	0.5 C-O	Pancreatectomized hydrocortisone	1–2‡
BC13	9	10	14–19	0.5 C-O	Pancreatectomized control	0
BC13	10	10	14–19	0.5 C-O	Pancreatectomized hydrocortisone	1–3‡

* Six birds in this group were sacrificed at age of 6 weeks, after five weeks on the experimental regimen.

† 0.5 and 1.0 C-O are chick starter mash supplemented with 0.5 and 1.0 per cent cholesterol (C) respectively and 5 per cent cottonseed oil (O).

‡ Dosage increased stepwise during course of experiment.

§ Regular ACTH, given in divided doses, twice daily.

¶ Long-acting ACTH (ACTHAR GEL), one dose per day.

‖ All hormones given parenterally.

the study. Serial blood samples were drawn and heparinized for determination of blood glucose,[16] plasma sodium and potassium,* plasma total cholesterol[17, 18] and lipid phosphorus.[19] At the preterminal bleeding, sera were also collected for ultracentrifugal analysis of circulating lipoproteins.[20-22]† Blood pressures were obtained just prior to sacrifice by direct puncture of a sciatic artery, utilizing the Lilly electromanometer and the Sanborn polyviso recorder. In a few birds of series BC 13, hematocrits (Wintrobe),[23] insulin tolerance tests[24] and eosinophil counts[23, 25] were done preterminally. The animals were killed by decapitation. Following complete autopsy, including determination of organ weights, thoracic and abdominal aortas were evaluated for gross atherosclerosis; subsequently, Sudan IV-stained frozen sections of the formalin-fixed hearts were studied microscopically for coronary lesions. The standardized methods of the department were utilized for grading gross aorta and microscopic coronary atherogenesis.[8, 26]

* Sodium and potassium were analyzed with the Beckman flame photometer.

† The ultracentrifuge analyses were accomplished by Drs. Lena Lewis and Irvine H. Page of the Cleveland Clinic Foundation. We gratefully acknowledge their cooperation in this conjoint effort. The ultracentrifuge data will be the subject of a separate communication.

RESULTS

1. *Plasma glucose and lipid levels* (*table 2*). Hydrocortisone induced a significant sustained hyperglycemia in cholesterol-fed cockerels, which tended to be more marked in the alloxanized, and most marked in the depancreatized birds. Glycosuria was observed in the more hyperglycemic chicks of the three compound F treated groups (groups 6, 8 and 10, series BC 13 and 15, table 2). These steroid-diabetic cockerels responded to insulin injection (0.5 unit per kilogram) with only a slight reduction in blood sugar levels, followed by a marked enhancement ("rebound") of hyperglycemia (table 3). Corticotropin (ACTH) and cortisone in large doses were without effect on glycemia in this study (table 2).*

* In a more recent experiment,[27] chicks treated for 20 days with long-acting corticotropin (ACTH) (ACTHAR GEL—25 mg. per bird per day parenterally) plus estrogens (mixed conjugated equine estrogens, Premarin, approximately 25 mg per bird per day orally) developed a definite hyperglycemia.[15, 63, 64] Corticotropin played a key role in

TABLE 2.—*Preterminal Blood Glucose and Lipid Levels*‡

Series	Group No.	Regimen*	Glucose mg. %	Total Cholesterol mg. %	Lipid Phosphorus mg. %	C/P Ratio†
BC9	1	Intact control	182 ± 2.3¶ 175–187§	260 ± 17 162–410	7.5 ± 0.4 5.6–11.3	36.1 ± 2.2 17.2–50.6
BC9	2	Intact cortisone	164 ± 2.7 158–173	287 ± 49 140–613	7.9 ± 0.5 5.6–9.3	29.0 ± 3.7 20.8–49.2
BC11	3	Intact control	161 ± 4.6 153–169	1037 ± 122 589–1492	17.5 ± 1.8 11.2–25.7	58.7 ± 2.9 48.0–71.7
BC11	4	Intact ACTH (6–8 mg.)	155 ± 7.7 125–192	1011 ± 118 528–1498	18.3 ± 1.2 11.8–22.8	53.9 ± 3.3 38.4–68.5
BC19	3	Intact control	217 ± 7.1 203–225	577 ± 40 465–705	12.0 ± 1.0 9.8–13.4	48.4 ± 1.4 44.3–52.5
BC19	4	Intact ACTH (10–25 mg.)	223 ± 2.5 218–234	1102 ± 189 598–1768	20.1 ± 2.0 15.3–26.4	53.3 ± 4.9 39.1–69.0
BC15	5	Intact control	172 ± 3.7 162–184	421 ± 57 256–598	10.9 ± 1.2 7.5–15.3	38.3 ± 1.9 32.5–44.1
BC15	6	Intact hydrocortisone	266 ± 29.3 214–395	722 ± 282 189–1397	16.9 ± 2.6 9.8–26.2	39.6 ± 5.9 19.3–61.8
BC15	7	Alloxanized control	175 ± 4.6 155–186	279 ± 41 182–388	8.9 ± 0.5 7.3–10.4	30.6 ± 3.5 23.6–38.5
BC15	8	Alloxanized hydrocortisone	308 ± 31.2 230–445	544 ± 76 370–785	17.7 ± 1.8 12.0–25.1	31.4 ± 3.9 17.7–42.0
BC15	9	Depancreatized control	198 ± 10.8 175–232	420 ± 67 226–634	9.7 ± 1.4 5.9–14.5	42.8 ± 1.9 38.3–48.8
BC15	10	Depancreatized hydrocortisone	371 ± 86.0 264–715	898 ± 213 220–1424	18.3 ± 3.4 8.5–26.8	46.3 ± 5.2 25.9–54.3

* See table 1 for details.

† C/P ratio is, $\frac{\text{total cholesterol}}{\text{lipid phosphorus}}$.

‡ Groups 9 and 10 of BC13 and BC15 exhibited essentially identical trends, hence only the latter are recorded here.

§ Range.

¶ Standard error of the mean.

Hydrocortisone and long-acting corticotropin (series BC 19) effected a sustained enhancement of lipemia (lactescence), hypercholesterolemia and hyperphospholipemia in cholesterol-fed cockerels (table 2).* The hormone-induced increases in plasma total cholesterol and lipid phosphorus were proportional, hence the plasma total cholesterol–lipid phosphorus (C/P) ratio was not altered. Cortisone and the lower dosage of regular corticotropin were without influence on plasma lipids.

ducing this hyperglycemia, since a control group receiving estrogen alone had normal blood glucose levels.

* In a subsequent study,[28] it was found that compound F also elicited lipemia, hypercholesterolemia and hyperphospholipemia in chicks fed a diet of plain mash, devoid of any cholesterol supplement.

TABLE 3.—*Insulin Tolerance Test*

Time after Insulin Injection* (min.)	Plasma Glucose	
	BC 13—Group 9 Depancreatized (mg. %)	BC 13—Group 10 Depancreatized + Hydrocortisone (mg. %)
Preinjection	186	258
15	159	227
30	157	282
45	166	342
60	167	387
90	182	434

* 0.5 unit of regular insulin.

2. *Blood pressure* and atherogenesis (table 4).* Cortisone apparently induced a moderate increase in the systolic and diastolic blood pressures of cholesterol-fed cockerels. Corticotropin apparently tended to exert a similar hypertensive effect, although to an even smaller degree. Limited data indicate no evidence of a blood pressure rise in depancreatized, steroid-diabetic (hydrocortisone-treated) birds. Cortisone apparently effected a moderate increase in the incidence of cholesterol-induced aorta and coronary atherogenesis in chicks, without intensifying the severity (grade) of aorta lesions (table 4). Neither corticotropin nor hydrocortisone had any demonstrable, definitive effect on atherogenesis in the two vascular beds studied. Data from two series (BC 13 and BC 15) suggest that compound F may partially inhibit coronary atherogenesis in depancreatized cockerels, but the findings are not definitive enough to permit any conclusion. Neither the diabetes nor the hyperadrenocorticism induced by hydrocortisone were associated with any intensification of cholesterol-induced aorta or coronary atherogenesis.

3. *Other findings (table 5).* Hydrocortisone consistently lowered plasma sodium levels, without affecting hematocrit, water intake, plasma potassium concentration or level of circulating eosinophils. Cortisone had no detectable influence on body fluids; the effects of corticotropin on these functions were not studied.

All experimental (hormone-treated) groups exhibited levels of feed intake equal to or in excess of their paired controls. Nevertheless, hydrocortisone markedly depressed rate of weight gain. Cortisone and corticotropin exerted this effect only minimally.

In conjunction with the moderate hypertension they developed (table 4), the cortisone-treated cockerels had an increase in the ratio heart weight–body weight. This phenomenon was not present in the corticotropin- or hydrocortisone-treated birds studied.

All three hormones, particularly cortisone, tended to have androgenic and/or gonadotrophic effects, as indicated by comb size indexes and testis weights in relation to body weights. Unexpectedly, neither cortisone nor hydrocortisone induced significant adrenal hypoplasia. The smaller dosage of corticotropin (series BC 11) did not effect definitive adrenal hyperplasia; no adrenal weight data were collected in series BC 19. Limited observations indicate no clearcut trend with respect to the influence of these hormones on thyroid weight.

DISCUSSION AND CONCLUSIONS

Despite their significant physiological effects, neither compound F nor corticotropin intensified aorta or coronary atherogenesis. Under these experimental conditions in chicks, therefore, neither hyperadrenocorticism nor steroid diabetes nor steroid-pancreatic diabetes was a gross aggravator of experimental cholesterol-induced atherogenesis.† These findings—unanticipated against the background clinical facts of intensified atherogenesis in man with hyperadrenocorticism and/or diabetes—are further noteworthy in view of the fact that these hormones effect a gross intensi-

* Our observations on the effects of steroids and corticotropin on blood pressure in chicks will be presented and discussed in greater detail in a separate communication.

† In contrast, preliminary findings suggest that chicks fed plain mash, devoid of a cholesterol supplement, may develop gross aorta atherosclerosis consequent upon long term exhibition of hydrocortisone.[28] Definitive information on this phenomenon awaits completion of experiments currently in progress.

TABLE 4.—*Blood Pressure and Atherogenesis*

Series and Group No.	Regimen	Pre-Terminal Blood Pressure mm. Hg	Gross Thoracic Aorta Atherogenesis		Microscopic Coronary Atherogenesis	
			Birds with Lesions %	Grade of Lesions	Birds with Lesions %	Coronary Count %
BC9—1	Intact control	§ 116 ± 7.5/102 ± 7.0 100–150/88–135¶	26	0.2 ± 0.07‖ 0.0–1.0¶	11	—
BC9—2	Intact cortisone	§ 138 ± 5.3/125 ± 5.2 115–153/103–140	75	0.6 ± 0.18 0.0–1.5	67	—
BC11—3	Intact control	134 ± 5.0/114 ± 4.9 124–140/105–122	100	2.0 ± 0.30 1.0–3.0	100	—
BC11—4	Intact ACTH (6–8 mg.)	146 ± 1.4/128 ± 2.4 141–150/123–140	100	2.1 ± 0.30 1.0–3.5	100	—
BC19—3	Intact control	—	100	1.5 ± 0.15 0.8–2.0	90	21.2 ± 4.4 0–43
BC19—4	Intact ACTH (10–25 mg.)	—	100	2.0 ± 0.23 0.8–2.8	60	14.7 ± 5.1 0–44
BC15—5	Intact control	—	75	1.1 ± 0.31 0.0–2.5	100	10.1 ± 2.4 3.3–20.0
BC15—6	Intact hydrocortisone	—	88	1.3 ± 0.34 0.0–3.0	88	8.8 ± 1.8 0–14
BC15—7	Alloxanized control	—	63	1.1 ± 0.41 0.0–2.8	100	8.8 ± 1.5 3–15
BC15—8	Alloxanized hydrocortisone	—	86	1.2 ± 0.34 0.0–2.5	100	12.8 ± 3.8 5–33
BC15—9*	Depancreatized control	146 ± 7.4/118 ± 4.8‡ 122–163/102–130	100	1.7 ± 0.28 0.5–3.0	77	10.8 ± 2.9 0–36
BC15—10*	Depancreatized hydrocortisone	147 ± 6.3/122 ± 5.0‡ 136–170/112–140	100	2.2 ± 0.18 1.8–2.5	59	4.2 ± 1.3 0–12

* Groups 9 and 10 of BC13 and BC15 exhibited essentially identical trends, hence only the latter are recorded here.

‡ Series BC13.

§ 6 weeks of age, 5 weeks on experimental regimen; at 11 weeks of age (10 weeks on experimental regimen) mean blood pressures of the control and cortisone groups were 142 ± 2.9 (range: 126–159) and 149 ± 5.2 (range: 119–164) respectively.

¶ Range.

‖ Standard error of the mean.

fication of cholesterol-induced lipemia, hypercholesterolemia and hyperphospholipemia. Several possible explanations may be hypothesized to account for the fact that this enhanced lipemia was not associated with any aggravating influence on atherogenesis. Thus, it may simply be due to the fact that the experimental cholesterol-supplemented diet was, of and by

TABLE 5.—*Other Findings*

1 Series and Group No.	2 Regimen	3 Plasma Na mEq/L.	4 Plasma K mEq/L.	5 H_2O Intake‡ cc./chick/day	6 Feed Intake‡ Gm./chick/day	7 Terminal Body Weight Gm.	8 Food Intake / Body Weight Gm./Kg./day	9 Heart Weight Gm.	10 Heart Weight / Body Weight mg./Gm.	11 Pre-terminal Comb Size Index	12 Testis Weight Gm.	13 Adrenal Weight mg.‡	14 Thyroid Weight mg.‡
BC9—1	Intact control	154.0†	6.3†	166	93	1070 ± 38.9§ 878–1276¶	87	5.16 ± 0.18 4.38–6.24	0.48	17 ± 3.2 9–27	0.88 0.15–2.33	50	46
BC9—2	Intact cortisone	153.2†	6.0†	129	131	893 ± 24.4 794–1077	147	5.33 ± 0.28 3.72–6.84	0.60	28 ± 5.0 16–43	1.98 0.21–4.53	46	48
BC11—3	Intact control	—	—	—	121	1705 ± 90.5 1247–2155	71	7.64 ± 0.31 7.03–9.11	0.45	32 ± 1.0 18–49	4.25 ± 0.92 0.71–9.30	80	—
BC11—4	Intact ACTH (6–8 mg)	—	—	—	125	1460 ± 43.4 1247–1673	86	7.25 ± 0.21 6.46–8.72	0.50	43 ± 6.5 22–94	7.92 ± 1.02 2.21–11.86	78	—
BC19—3	Intact control	—	—	—	111	1950 ± 45 1839–2038	57	—	—	—	—	—	—
BC19—4	Intact ACTH (10–25 mg)	—	—	—	110	1967 ± 72 1812–2264	56	—	—	—	—	—	—
BC15—5	Intact control	163.5 ± 1.2 160.2–167.0	5.12 ± 0.36 4.40–6.30	242	198	1799 ± 28 1697–1896	113	—	—	48 ± 5.4 35–70	—	63	—
BC15—6	Intact hydrocortisone	150.6 ± 2.2 144.2–158.8	4.54 ± 0.13 3.98–4.84	205	141	1189 ± 22 1132–1274	137	—	—	46 ± 6.1 18–68	—	51	—
BC15—7	Alloxanized control	162.7 ± 1.5 159.0–169.0	4.84 ± 0.07 4.64–5.02	259	176	1790 ± 90 1590–2320	92	—	—	63 ± 6.3 44–94	—	74	—
BC15—8	Alloxanized hydrocortisone	144.9 ± 1.2 140.6–147.0	4.57 ± 0.15 4.12–5.56	181	138	1359 ± 58 1245–1472	101	—	—	46 ± 10.0 17–63	—	64	—
BC13—9* and 15	Depancreatized control	166.6 ± 2.2 159.4–171.2	5.33 ± 0.19 4.92–6.04	307	161	1624 ± 71 1443–1839	86	9.10	0.49	52 ± 76 25–67	5.70	91	80
BC13—10* and 15	Depancreatized hydrocortisone	144.5 ± 2.1 139.4–151.4	4.26 ± 0.11 3.98–4.68	200	154	1029 ± 90 879–1189	147	5.40	0.51	40 ± 9.3 18–55	5.10	53	44

* Combined data from BC13 and BC15; findings in two series were consistent throughout.
† Pooled sample.
¶ Range.
§ Standard error of the mean.

itself, maximally atherogenic, thereby masking any hormonal propensity to intensify atherogenesis (with respect to this possibility, see the preceding footnote). Alternatively, the particular pattern of hydrocortisone- and corticotropin-induced enhancement of lipemia may account for absence of aggravated atherogenesis; e.g. the pattern of plasma total cholesterol–lipid phosphorus (C/P) ratios (which did not rise under hormonal influence) or the pattern of plasma lipoprotein classes. A third hypothetic explanation is that local corticoid effects on the arterial wall[29-37] may have afforded counter-protection to any atherogenesis-intensifying effect possibly resulting from the corticoid influences on lipemia. Finally, it is possible that the specific effects on other endocrine organs, elicited by hydrocortisone or corticotropin exhibition,[30] may act to prevent aggravation of atherogenesis despite increase of lipemia. Obviously, the data of the present experiments do not afford any basis for scientific choice among these and other possibilities.

In contrast to compound F and corticotropin, cortisone apparently intensified both coronary and aorta atherogenesis, without significantly influencing lipemia or other metabolic functions in this avian species. It may be that this intensified atherogenesis induced by compound E was—as would also appear to be the case with desoxycorticosterone acetate (DCA)[8, 9]—a resultant of the moderate steroid-induced increase in blood pressure.

Both experimental and clinical atherogenesis are apparently related intimately to the overall metabolic state of the organism. Hence, it was deemed essential in these experiments to delineate some of the specific metabolic effects of these hormones in this avian species, in the hope that light might thereby be cast upon the mode of their action in atherogenesis. As already indicated, hydrocortisone had marked physiologic activity in chicks, whereas cortisone was relatively inert.* Thus, moderate doses of compound F—in contrast to compound E—elicited multiple evidences of marked hyperadrenocorticism in cockerels. These included alterations in electrolyte, lipid, carbohydrate and protein metabolism, biochemical-physiologic effects which were, for the most part, similar to those elicited in mammals (including man) by the 11,17-oxysteroids.[29-41]†

Corticotropin in large doses also produced moderate hyperadrenocorticism in chicks.[42] The metabolic alterations induced by corticotropin, particularly the increase of lipemia, resembled those effected by hydrocortisone, suggesting that compound F was a significant component of the steroid moiety endogenously secreted by the corticotropin-stimulated adrenal cortex of the bird. Similarly, strong evidence is available that hydrocortisone is a major physiologic secretory product of the adrenal cortex of mammals, including man.[38-41, 43-48] Thus, it would appear that there are more similarities than differences between avian and mammalian species in the endocrinology of the adrenal cortex.

The finding that corticotropin and compound F increased lipemia, hypercholesterolemia and hyperphospholipemia in cholesterol-fed chicks is in accord with data collected by others in rabbits[49-53] and (in some cases) in man.[38, 39, 54-56] These recent observations represent significant additions to the meager knowledge of corticoid influences on lipid metabolism, an aspect of adrenal cortical physiology that has received only limited attention.[29-36, 57-59] Little is known about the mechanism of the lipemia induced by 11,17-oxysteroids. It has been shown that the pituitary-adrenal system plays an important part in the mobilization of depot fat to the liver.[60] Further, it has recently been demonstrated that cortisone increases the rate of incorporation of acetate into cholesterol by

* In contrast to its activity in mammalian species,[29-31] cortisone failed to exert a gross influence on carbohydrate, lipid, electrolyte or protein metabolism in chicks. The major physiologic effect observed was androgenic and/or gonadotrophic. The biochemical basis for this difference between mammalian and avian species is not presently apparent. It may be related to differences between avian and mammalian organism in ability to convert exogenous cortisone into hydrocortisone.[45-47]

† As in mammals, the mineralo-corticoid desoxycorticosterone grossly influenced only water and electrolyte metabolism in chronic experiments in chicks.[4, 8, 9]

* Combined data from BC13 and BC15; findings in two series were consistent throughout.
† Pooled sample.
‡ Range.
§ Standard error of the mean.

the perfused rat liver,[61] whereas hypophysectomy markedly depresses hepatic ability to convert acetate to cholesterol.[62]

Further work is essential to elucidate the precise sites and modes of influence of these and other hormones on lipid metabolism. Such studies are vital for the final solution of the atherosclerosis problem.

Summary

1. Hydrocortisone (compound F) in moderate doses induced marked sustained hyperadrenocorticism in cholesterol-fed cockerels (intact, alloxanized and depancreatized), including typical 11,17-oxysteroid effects on carbohydrate, protein, lipid and electrolyte metabolism. Despite steroid-induced diabetes and enhancement of hypercholesterolemic hyperlipemia, no intensification of aorta or coronary atherogenesis supervened.

2. Long-acting corticotropin in large doses induced moderate sustained hyperadrenocorticism in cholesterol-fed cockerels, with a pattern of biochemical-physiologic-pathologic alterations similar to that effected by compound F.

3. Cortisone in large doses was relatively inactive in this avian species, exerting no significant effects on carbohydrate, protein, lipid or electrolyte metabolism. No increase of hypercholesterolemic hyperlipemia was observed. Nevertheless, moderate intensification of aorta and coronary atherogenesis occurred, in association with moderate hypertensive effects induced by this corticoid in chicks.

Sumario Español

1. Hidrocortisona (compuesto F) en dosis moderadas indujo marcado y sostenido hiperadrenocorticismo en gallipollos alimentados con colesterol (intactos, aloxinados y depancreatizados), incluyendo los efectos típicos en el metabolismo electrolítico, de proteínas, carbohidrato y lípidos de 11, 17-oxiesteroides. No obstante la diabetis inducida por los esteroides y el acrecentamiento de la hiperlipemia hipercolesterolémica, no supervino intensificación de la aterogénesis coronaria o de la aorta.

2. Corticotropina de acción prolongada en dosis grandes indujo hiperadrenocorticismo moderado sostenido en gallipollos alimentados con colesterol, con un patrón de alteraciones fisiopatológicas y bioquímicas similares a las producidas por el compuesto F.

3. La cortisona en dosis grandes fué relativamente inactiva en estas especies aviarias, no ejerciendo efectos significativos en el metabolismo de carbohidratos, proteínas, lípidos o electrolitos. No se observó acrecentamiento de la hiperlipemia hipercolesterolémica. No obstante ocurrió intensificación de la aterogénesis coronaria y de la aorta, en asociación a los moderados efectos hipertensos inducidos por este corticoide en los polluelos.

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Estrogen Prophylaxis of Cholesterol-Induced Coronary Atherogenesis in Chicks Given Adrenal Corticoids or ACTH

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Estrogen prophylaxis of experimental cholesterol-induced coronary atherogenesis in cockerels is unimpaired by the hyperadrenalism and steroid diabetes variously produced by concomitant exhibition of desoxycorticosterone acetate (DCA), hydrocortisone, cortisone or adrenocorticotropic hormone (ACTH).

PREVIOUS work from this department demonstrated that estrogens inhibit coronary atherogenesis in cholesterol-fed cockerels.[1-4] The present study shows that estrogen prophylaxis of coronary atherogenesis is unimpaired by concomitant exhibition of adrenal steroids or adrenocorticotropic hormone (ACTH). It thereby serves to clarify certain problems of the mechanism of the estrogen effect.

METHODS

The experimental designs and techniques were generally in accord with the standardized procedures established in this department.[4, 5] Two series of experiments were completed, utilizing a total of 80 cockerels (table 1). The precise biochemical, nutritional, physiologic and pathologic methods employed were detailed in the previous paper.[5]

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This work was done during Dr. Stamler's tenure of a Fellowship as an Established Investigator of the American Heart Association.

RESULTS

The experimental findings are summarized in tables 2 and 3. None of the hormone regimens effected an elevation of blood pressure. Thus, the estrogens apparently counteracted

TABLE 1.—*Experimental Regimens*

Series	Group	Number of Chicks	Chick Age During Experiment Weeks	Diet	Hormone*
BC 20	1	10	12–19	1 CO†	None
BC 20	2	10	12–19	1 CO	Estrogens
BC 20	3	10	12–19	1 CO	Estrogens + DCA
BC 20	4	10	12–19	1 CO	Estrogens + Cortisone
BC 20	5	10	12–19	1 CO	Estrogens + Hydrocortisone
BC 23	1	10	7–13	1 CO	None
BC 23	2	10	7–13	1 CO	Estrogens
BC 23	6	10	7–13	1 CO	Estrogens + ACTH

* Hormone dosages were: *Estrogens* (mixed conjugated equine estrogens), approximately 25–30 mg./chick/day in the drinking water. *DCA* (desoxycorticosterone acetate), 1–5 mg./chick/day parenterally in oil. *Cortisone*, 5–20 mg./chick/day parenterally in saline suspension. *Hydrocortisone*, 1–4 mg./chick/day parenterally in saline suspension. *ACTH*, 25 mg./chick/day parenterally of a long-acting preparation.

Steroid dosages were increased stepwise at the end of the second, fourth and fifth experimental weeks.

† 1 CO is chick starter mash + 1 per cent cholesterol + 5 per cent cottonseed oil.

TABLE 2.—*Blood Pressure, Plasma Preterminal Lipid Levels and Atherogenesis*

Series and Group	Regimen	Mean Blood Pressure mm. Hg	Total Cholesterol mg.%	Lipid P mg.%	C/P Ratio*	Gross Thoracic Aorta Atherogenesis		Microscopic Coronary Atherogenesis	
						Birds with Lesions %	Grade of Lesions	Birds with Lesions %	Coronary Count† %
BC 20 1	1 CO	149 ± 3.2§ 140–162‡	573 ± 66.1 362–791	15.1 ± 1.0 11.5–16.6	37.7 ± 3.1 31.5–47.7	100	1.4 ± 0.2 0.3–2.5	80	15.9 ± 3.6 0.0–33.3
BC 20 2	1 CO + Estrogens	142 ± 33.3 134–156	692 ± 38.4 530–782	53.7 ± 6.7 33.8–74.6	13.7 ± 1.5 10.5–20.6	100	1.6 ± 0.2 0.8–3.0	13	1.9 ± 1.0 0.0–13.1
BC 20 3	1 CO + Estrogens + DCA	150 ± 3.4 136–160	1085 ± 100.4 728–1394	111.5 ± 11.3 76.7–147.1	9.9 ± 0.6 8.2–12.1	100	1.4 ± 0.2 0.8–3.0	11	1.5 ± 0.9 0.0–13.3
BC 20 4	1 CO + Estrogens + Cortisone	132 ± 6.7 116–162	1115 ± 86.5 915–1375	119.6 ± 11.7 89.6–159.6	9.4 ± 0.2 8.5–10.2	100	1.7 ± 0.3 1.0–3.0	0	0
BC 20 5	1 CO + Estrogens + Hydrocortisone	139 ± 0.8 136–142	1061 ± 98.0 776–1391	83.4 ± 7.6 69.2–117.1	13.0 ± 1.3 8.8–17.3	100	1.9 ± 0.2 0.8–3.0	25	3.0 ± 2.5 0–20.0
BC 23 1	1 CO	—	1028 ± 102.0 679–1715	19.1 ± 1.4 14.5–27.7	53.4 ± 2.8 42.4–65.9	100	2.1 ± 0.2 1.3–2.5	100	24.8 ± 2.1 15.0–33.3
BC 23 2	1 CO + Estrogens	—	599 ± 44.3 342–1092	49.6 ± 11.1 19.4–107.0	14.8 ± 1.6 7.8–23.6	100	1.4 ± 0.2 0.3–2.5	30	5.6 ± 3.2 0.0–29.4
BC 23 6	1 CO + Estrogens + ACTH	—	839 ± 86.4 511–1445	59.4 ± 5.2 35.4–82.8	14.6 ± 1.2 8.2–20.2	100	2.5 ± 0.2 1.5–3.5	30	2.7 ± 1.7 0.0–16.1

* C/P ratio is the plasma $\frac{\text{total cholesterol}}{\text{lipid phosphorus}}$ ratio.

† Coronary count is the percentage of arteries and arterioles exhibiting microscopic atheromatous or atherosclerotic lesions.

‡ Range.

§ Standard error of the mean.

TABLE 3.—*Other Findings*

Series and Group	Regimen	H_2O Intake* cc./bird/day	Feed Intake* Gm./chick/day	Terminal Weight Gm.	Comb Index
BC 20 1	1 CO	320	143	2278 ± 137† 1867–2858	43.0 ± 8.7 26–73
BC 20 2	1 CO + Estrogens	502	136	2316 ± 47 2208–2519	13.5 ± 0.9 12–16
BC 20 3	1 CO + Estrogens + DCA	600	121	1909 ± 59 1697–2094	16.6 ± 2.4 11–22
BC 20 4	1 CO + Estrogens + Cortisone	638	167	1839 ± 115 1472–2264	15.0 ± 2.9 10–25
BC 20 5	1 CO + Estrogens + Hydrocortisone	667	142	1545 ± 45 1386–1697	12.0 ± 0.8 9–13
BC 23 1	1 CO	—	157	1604 —	41.0 ± 6.6 25–55
BC 23 2	1 CO + Estrogens	—	149	1338 —	6.0 ± 0.8 4–8
BC 23 6	1 CO + Estrogens + ACTH	—	150	1087 —	4.5 ± 0.7 3–6

* Fourth experimental week; data were collected on the group as a unit.
† Standard error of the mean.

the hypertensive influence of desoxycorticosterone acetate and cortisone.[4-6]

All groups receiving estrogens, with or without other hormone, exhibited the typical triad of estrogen effects,[1-5] i.e. feminization (low comb indexes), marked enhancement of hyperphospholipemia (with resultant reduction of plasma total cholesterol–lipid phosphorus ratios to normal levels), and prophylactic inhibition of coronary atherogenesis (with no effect on aorta atherogenesis). Thus, none of the estrogen effects were counteracted by concomitant exhibition of steroids or corticotropin in the dosages used.

All steroid-treated groups exhibited retardation of growth and development despite normal feed intake; this phenomenon was most marked in the groups receiving hydrocortisone and corticotropin, respectively. All chicks given hormone developed moderate polydypsia (table 3). Blood sugar determinations on the twentieth experimental day revealed hyperglycemia in the cockerels receiving estrogens plus corticotropin; mean blood glucose value in these chicks was ± 37.6 mg. per 100 cc., range 193–425 (control ± 8.4, range 151–178 mg. per 100 cc.).

Discussion and Conclusions

Estrogen prophylaxis of cholesterol-induced coronary atherogenesis in cockerels continues to operate effectively when adrenal corticoids or ACTH is concomitantly administered. Thus, the estrogen effect is not reversed by hyperadrenocorticism or steroid diabetes, or by the multiple influences of the pituitary-adrenal hormones on metabolism, vascular permeability, connective tissue function, and similar effects.[5]

The findings in this experiment further suggest that estrogen inhibition of cholesterol-induced coronary atherogenesis is not mediated indirectly, via a possible estrogen-induced suppression of the pituitary corticotropin-adrenal corticoid secretion.[5] This observation supplements a previous conclusion of ours that the estrogen effect cannot be attributed to estrogen-induced suppression of

pituitary gonadotropic-testicular androgen secretion.[3] The mechanism of the estrogen effect on atherogenesis remains to be elucidated.

Summary

Estrogen prophylaxis of cholesterol-induced coronary atherogenesis in cockerels is unimpaired by concomitant exhibition of adrenal steroids or ACTH.

Sumario Español

La profilaxis con estrógeno de la aterogénesis coronaria en gallipollos es inalterada por el hiperadrenalismo y la diabetis esteroidea variablemente producida por el uso concomitante de acetato de desoxicorticosterona (DCA), hidrocortisona, cortisona o la hormona adrenocorticotrófica (ACTH).

Acknowledgments

The accomplishment of these experiments was possible only by virtue of the excellent services rendered by the technician members of the department's atherosclerosis research team, including Christine Bolene Williams,* Grady Crowley, Marilyn Dudley (deceased), Dolores Friedman, Philip Johnson, Chizuko Kakita, Mildred Michael, John Morris and Ronald Wallace. It is also a pleasure to acknowledge the assistance of Bernice Huddleston of the Department of Metabolism and Endocrinology, who carried out the glucose analyses for this experiment.

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Inhibition of Cholesterol-Induced Coronary Atherogenesis in the Egg-Producing Hen

By JEREMIAH STAMLER, M.D., RUTH PICK, M.D., AND LOUIS N. KATZ, M.D.

Mature egg-producing hens, intact or after oviduct ligation, are markedly resistant to cholesterol-induced coronary atherogenesis. This inhibition of coronary atherosclerosis is apparently effected by the endogenous estrogen secretion of these female birds.

PREVIOUS work in this department demonstrated that oral or parenteral administration of estrogens inhibits coronary atherogenesis in cholesterol-fed cockerels.[1-3] The present study was undertaken to determine whether the *endogenous* estrogen secretion of the egg-producing hen has a similar prophylactic effect.

METHODS

The experimental designs and technics were generally in accord with the standardized procedures developed by the department's atherosclerosis research group.[3] Altogether, four series of chronic experiments were completed, varying in duration from 5 to 11 weeks, and utilizing a total of 129 fully grown, sexually mature chickens, age 24 to 34 weeks at the onset of the study (table 1). Essentially, a comparison was made of the plasma lipid and atherogenic (aortic and coronary artery) response to cholesterol feeding in mature female vs. male chickens. All hens were laying eggs before the experiment began; they exhibited the typical plasma lipid pattern resulting from endogenous estrogen secretion by the ovary associated with egg production (table 2).[3, 4] In series BC 22, based on the plasma lipid findings in the earlier series (table 3), a greater dietary atherogenic stimulus was imposed upon the hens than upon the roosters, by feeding the females a mash containing twice as much cholesterol (2 per cent) as that given the males (1 per cent) (table 1). In series BC 20 and BC 22, the removal from the body of large quantities of cholesterol and lipid via egg-laying was countered in one group of females by ligation of the oviduct. These hens continued to produce egg yolks which were deposited from the ovary into the peritoneal cavity. It is probable that at least partial absorption and recirculation of the lipoprotein material occurred.

The specific nutritional, biochemical, physiologic and pathologic methods employed in studying these birds were detailed in a previous paper.[5]

RESULTS

Plasma Lipids. When fed the same diet as roosters, intact hens consistently exhibited lower plasma total cholesterol levels despite essentially similar feed intakes and despite the hyperlipemic influence of the endogenous estrogen secretion (series BC 15 and BC 18, table 3). Intact females eating a 2 per cent cholesterol diet (2 CO) exhibited plasma total cholesterol levels essentially similar to those of males ingesting a 1 CO mash (groups 1 and 2, series BC 20 and BC 22, table 3). Thus, to achieve levels of hypercholesterolemia in egg-laying hens equal to those in roosters, females had to ingest twice as much cholesterol (since levels of feed intake were practically identical). This less marked hypercholesterolemic response of the hen to cholesterol feeding was apparently a by-product of egg laying, since it was virtually abolished by oviduct ligation, which significantly enhanced hypercholesterolemia in both series BC 20 and BC 22 (group 4, table 3; data from these two series are combined in this table). Administration of estrogens to roosters markedly intensified hypercholesterolemia in this experiment (group 3, series BC 22, table 3).

In all series, hens (both intact and with ligated oviducts) exhibited grossly increased plasma lipid phosphorus levels with low or

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This work was done during Dr. Stamler's tenure of a Fellowship as an Established Investigator of the American Heart Association.

TABLE 1.—*Experimental Regimens*

Series	Group	Number of Birds	Sex	Age Weeks	Diet	Other Procedure
BC 15	1	11	Male	34–44	2 CO*	—
	2	7	Female	34–44	2 CO	—
BC 18	1	15	Male	28–33	2 CO	—
	2	24	Female	28–33	2 CO	—
	1A	22	Male	28–39	2 CO	—
	2A	13	Female	28–39	2 CO	—
BC 20	2	4	Female	28–33	2 CO	—
	4	4	Female	28–33	2 CO	Oviduct ligation
BC 22	1	8	Male	24–29	1 CO*	—
	2	8	Female	24–29	2 CO	—
	3	8	Male	24–29	1 CO	Estrogens†
	4	5	Female	24–29	2 CO	Oviduct ligation

* 1 CO and 2 CO are chick starter mash supplemented with 5% cottonseed oil (O) and 1%, 2% cholesterol respectively.

† 20–30 mg./chick/day of mixed conjugated equine estrogens (Premarin) in drinking water.

normal plasma total cholesterol–lipid phosphorus (C/P) ratios. This plasma lipid pattern, resulting from endogenous estrogen secretion in egg-producing females, was also noted in males receiving oral estrogens (group 3, series BC 22, table 3).

Coronary Artery and Aorta Atherogenesis. In all series, hens (intact and oviduct-ligated) exhibited marked inhibition of coronary artery atherogenesis. In accord with previous findings,[1, 3] estrogen-treated roosters also exhibited this phenomenon (group 3, series BC 22, table 3). All groups—untreated males, estrogen-treated males, intact females and oviduct-ligated females—exhibited similar incidences and gradings of cholesterol-induced thoracic aorta atherosclerosis.

DISCUSSION AND CONCLUSIONS

Sexually mature chickens exhibit a significant sex difference in susceptibility to experimental cholesterol-induced coronary

TABLE 2.—*Plasma Lipid Levels in Mature Male and Female Chickens Fed Plain Mash, without Cholesterol or Oil Supplement*

Series	Sex	Age	Number of Birds	Total Cholesterol mg. %	Lipid Phosphorus mg. %	C/P Ratio*
BC 15	Male	—	—	—	—	—
	Female	33	6	166 ± 31.5§	45.5 ± 9.0	3.7 ± 0.1
				71–261‡	16.7–70.7	3.4–4.2
BC 18	Male	28	6	98 ± 8.9	9.7 ± 0.4	10.0 ± 0.8
				78–138	8.2–11.1	8.8–13.7
	Female	28	8	88 ± 6.1	14.6 ± 2.3	6.8 ± 0.9
				63–108	8.7–27.0	3.1–9.6
BC 20	Male†	28	6	98 ± 8.9	9.7 ± 0.4	10.0 ± 0.8
				78–138	8.2–11.1	8.8–13.7
	Female	26	4	124 ± 20.2	24.1 ± 5.5	5.9 ± 1.2
				83–169	8.8–34.1	3.8–9.4

* C/P Ratio is the ratio $\frac{\text{plasma total cholesterol}}{\text{plasma lipid phosphorus}}$.

† Data from previous experiment, BC 18

‡ Range.

§ Standard error of the mean.

TABLE 3.—*Results: Plasma Lipids and Atherogenesis*

Series	Groups	Sex	Total Cholesterol mg. %	C/P Ratio*	Gross Thoracic Aorta Lesions		Microscopic Coronary Lesions	
					Birds with Lesions %	Grade of Lesions	Birds with Lesions %	Coronary Count¶ %
BC 15‖	1	Male	418 ± 38.4††	34.8 ± 2.4	86	1.2 ± 0.5	71	—
			157–699**	24.4–50.4		0.0–4.0		
	2	Female	252 ± 24.2	8.4 ± 0.7	60	0.4 ± 0.1	0	—
			167–390	6.2–14.1		0.0–0.8		
BC 18‖	1	Male	542 ± 62.5	39.8 ± 3.5	100	1.4 ± 0.2	80	17 ± 4.3
			192–1172	31.4–51.4		0.8–2.0		0–39
	2	Female	314 ± 37.1	16.5 ± 2.7	33	0.1 ± 0.1	11	1 ± 0.8
			77–800	8.5–28.3		0.0–0.3		0–7
	1A	Male	588 ± 57	45.9 ± 1.9	100	1.6 ± 0.2	90	11 ± 2.3
			192–1172	31.4–64.7		0.3–3.5		0–26
	2A	Female	288 ± 29	12.7 ± 1.7	61	0.6 ± 0.2	20	1 ± 0.9
			77–800	6.5–28.3		0.0–2.8		0–7
BC 20‖ and BC22‖	1	Male	235 ± 23.9	31.3 ± 2.7	75	0.7 ± 0.2	57	6 ± 3.5
			130–380	18.4–50.0		0.0–1.3		0–26
	2†	Female	286 ± 32.2	8.7 ± 0.9	64	0.4 ± 0.1	27	3 ± 1.6
			100–614	4.9–24.1		0.0–1.0		0–17
	3‡	Male	1136 ± 75.5	11.4 ± 0.9	88	1.0 ± 0.3	14	1 ± 0.4
			788–1528	8.4–18.7		0.0–2.0		0–6
	4§	Female	490 ± 52	12.3 ± 1.5	56	0.5 ± 0.2	13	0.5 ± 0.5
			231–971	6.6–21.1		0.0–1.0		0–4

* C/P Ratio is the ratio, $\frac{\text{plasma total cholesterol}}{\text{plasma lipid phosphorus}}$.

† BC 20 and BC 22 combined (12 hens).

‡ Estrogen-treated group.

§ Oviduct ligated groups, BC 20 and BC 22 combined (9 hens).

¶ Coronary count is the ratio, $\frac{\text{vessels with lesions}}{\text{total vessels examined}}$.[3]

‖ Plasma lipid data are the means of values obtained at the following experimental periods:
BC 15—Weeks 1, 3, 5, 9 and 10
BC 18—Groups 1 and 2—Weeks 1, 3 and 5
BC 18—Groups 1A and 2A—Weeks, 1, 3, 5, 6 and 11
BC 20—Weeks 1, 3 and 5
BC 22—Weeks 1 and 5

** Range.

†† Standard error of the mean.

atherogenesis. This marked resistance of hens to coronary atherosclerosis apparently cannot be attributed to disposal ("clearing") of cholesterol from the body via egg laying, since it is present in oviduct-ligated, as well as in intact females.

This sex difference in coronary atherogenesis is *not* present in immature chicks. Previous studies in this department demonstrated that sexually immature male and female chicks exhibit an identical susceptibility to experimental cholesterol-induced coronary atherogenesis.[7, 8]

The resistance to coronary atherogenesis in egg-producing, cholesterol-fed hens is associated with enhancement of hyperphospholipemia, lowering of plasma total cholesterol–lipid phosphorus ratios to normal levels and susceptibility to aorta atherogenesis. This response pattern in hens is identical with that produced by oral or parenteral exhibition of *exogenous* estrogens to cholesterol-fed cockerels, roosters and immature female chicks.[1-3, 6, 7]

All these findings indicate that inhibition of cholesterol-induced coronary atherogenesis in hens is effected by endogenously secreted ovarian estrogens.

In our original study on the effects of estrogens on cholesterol-induced atherosclerosis, an empiric method was utilized to establish

the dosage of 1 mg. per chick per day of parenteral estradiol. A preliminary acute experiment on cockerels fed plain mash was carried out in which a range of estradiol dosages was tested for their effects on plasma lipids. A dosage of 1 mg. per chick per day was selected because this was the minimum amount of estradiol capable of reproducing the plasma lipid pattern of the egg-laying hen. It was estimated that this dosage approximated the physiologic daily estrogen secretion in the mature female. The results of the present experiment on hens—both with respect to plasma lipid patterns and atherogenesis—reinforce the foregoing conclusion from our original assay, based exclusively on plasma lipid responses in the cockerel fed plain mash. Physiologic (not so-called pharmacological) dosages of estrogen, exogenous or endogenous, are capable of protecting the coronary arteries of male and female chickens against cholesterol-induced atherogenesis.

It is noteworthy that mature, gonadally-active chickens and humans both exhibit a marked sex differential—in favor of the female of the species—in susceptibility to coronary atherosclerosis. The findings of the present experiment lend further support to the presumptive conclusion from our previous studies[1-3] that estrogens may play a key role in protecting premenopausal women against coronary atherogenesis.

Summary

Mature egg-producing hens, intact or with ligated oviducts, are markedly resistant to cholesterol-induced coronary atherogenesis. This inhibition of coronary atherosclerosis is apparently effected by the endogenous estrogen secretion of these female birds.

Sumario Español

Gallinas adultas productoras de huevos, intactas o luego de la ligadura del oviducto, son marcadamente resistentes a la aterogénesis coronaria inducida por colesterol. Esta inhibición de la ateroesclerosis coronaria es aparentemente producida por la secreción endógena de estrógeno de estas aves hembras.

Acknowledgments

The accomplishment of these experiments was possible only by virtue of the excellent services rendered by the technician members of the department's atherosclerosis research team, including Christine Bolene Williams,* Grady Crowley, Marilyn Dudley (deceased), Dolores Friedman, Philip Johnson, Chizuko Kakita, Mildred Michael, John Morris and Ronald Wallace. It is a pleasure to express our gratitude to Dr. John B. Jewell and Dr. Stanley Jaros of Ayerst, McKenna and Harrison, Ltd. for the generous supplies of Premarin made available to us for this and other studies.

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Prolonged Observations of the Cardiovascular Status in Essential Hyperlipemia

With Special Reference to Serum Lipid Response to Heparin

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Study of the natural course of essential hyperlipemia discloses that this disease is frequently associated with premature atherosclerosis. It is, therefore, our contention that we can no longer regard essential hyperlipemia as a benign disease. Heparin administered intravenously to patients with essential hyperlipemia produces dramatic though transient lowering of total lipids. This is due predominantly to heparin's effect upon neutral fat. Normal controls show no significant differences in their lipid response to heparin, though of course the degree of these changes is comparatively smaller.

CONTINUAL observation of the clinical course of essential hyperlipemia prompts us to state that, contrary to previous concepts,[1] it is no longer tenable to believe that this is a benign disease. The evidence presented below illustrates that premature atherosclerosis is found in essential hyperlipemia, and that when present it is associated with hypercholesterolemia.

Essential or idiopathic hyperlipemia is characterized by serum which contains an abnormally large amount of neutral fat and which may therefore, on standing, appear grossly milky. There usually is, but need not necessarily be, elevated serum levels of cholesterol, cholesterol esters, and phospholipids. Hyperlipemia is called essential when it is found in the absence of diseases which are known to be associated with a secondary hyperlipemia. These diseases are diabetes mellitus, lipid nephrosis, the nephrotic stage of glomerulonephritis, thrombosis of the renal veins, pancreatitis, hepatic disease, obstructive jaundice, poisoning, pregnancy, anemias, anoxemia, Von Gierke's disease, cachexia and Niemann-Pick disease. Myxedema has been considered to be one of the causes of secondary hyperlipemia, but it has been our experience that myxedema is characterized by hypercholesterolemia alone rather than by an associated elevation of neutral fat. It is Thannhauser's[2] contention that the hyperlipemia of essential hyperlipemia is a retention phenomenon rather than a manifestation of increased lipid production or transportation. We studied a group of seven patients with essential hyperlipemia for periods of one to four years with special and periodic examinations for early or occult cardiovascular disease. Serum lipid analyses were made frequently and the effect of heparin as an antilipemic agent and as a therapeutic tool was investigated.

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METHOD AND MATERIAL

Seven patients, six men and one woman, were studied for a period of from one to four years. The present ages of the patients ranges from 35 to 61 years with an average age of 46.1 years. Three healthy subjects ages 28 to 43, two men and one woman, were controls. Lipid analyses were done and the methods used were as follows: for cholesterol and cholesterol esters, that of Bloor and Knudson[3]; for fatty acids, that of Stoddard and Drury[4]; for lipid phosphorus, that of Youngburg and Youngburg[5], using the method of Fiske and SubbaRow.[6] The total lipids were determined gravimetrically according to the method of Rubin.[7] The Moreton nepholometric method[8] of measuring chylomicrons was used and the results or turbidity indexes are reported as Moreton units. If the resting electrocardiogram was normal and symptoms were suggestive of angina pectoris, exercise electrocardiograms were done according to our modified two-step test method.[9-10] Ballistocardiograms were performed in many instances, using a high-frequency table. In patients with probable intermittent claudi-

TABLE 1.—*Lipid Analyses of Essential Hyperlipemia Patients after Heparin*

Pt.	Date	Hour	TL	FA	NF	C	CE	P	T	Date	Hour	TL	FA	NF	C	CE	P	T
L. W.	1953	Fasting	4037	3484	2930	464	304	400	11300	1950	Fasting	2815	2305	1569	338	219	920	
		1	2860	2244	1830	418	286	361	9700		2	1740	1181	808	311	186	367	
		2	2807	2214	1825	410	256	361	6100		4	1488	944	639	276	163	290	
		3	2469	1918	1570	392	240	310	6100									
		24	5385	4724	4390	400	250	390	13700									
E. I.	1953	Fasting	1717	1255	881	300	200	366		1950	Fasting	2385	1520	1115	435	280	310	
		1	1148	679	276	336	224	353			4	1365	709		407	244		
		2	1060	641	257	290	214	338										
		3	1030	517	146	380	174	363										
		24	1392	945	536	300	230	368										
G. T.	Oct. 1953	Fasting	859	458	134	293	170	293	72	March 1953	Fasting	2242	1358	599	608	447	672	544
		1	843	428	77	303	193	305	38		1	1967	1078	408	598	410	625	315
		2	831	458	80	290	193	303	35		2	1843	1019	276	598	432	617	270
		3	851	472	166	260	158	285	45		3	1711	945	225	544	407	610	293
		24	867	502	180	254	167	297	38		24	2546	1624	865	620	452	692	580
A. T.	1953	Fasting	1467	797	197	520	420	407	63	1950	Fasting	1700	517	51	576	370	261	
		1	1559	886	288	528	448	378	17									
		2	1650	915	316	584	440	390	18									
		3	1590	886	342	560	380	378	22									
		24	1667	886	259	620	440	428	38									
H. O.	1953	Fasting	1564	1033	628	400	270	315	98	1950	Fasting	1112	561	204	379	275	215	
		1	1320	738	274	440	290	368	56		2	891	295	0	411	218	215	
		2	1216	694	296	400	252	315	37		4	1036	376	0	411	243	275	
		3	1207	723	342	380	276	260	79									
		24	1398	871	439	380	258	368	99									
C. P.	1953	Fasting	2177	1328	680	682	479	425	630	1950	Fasting	1398	723	258	426	307	342	106
		1	1982	1033	348	768	533	403	530		1	1195	482	17	406	294	350	75
		2				768	544	392	310		2	1280	465	0	430	306	600	62
		3	1938	1078	422	704	501	402	320		4	1055	474	0	406	206	363	61
		24	2429	1506	800	724	511	486	635									
H. T.	Feb. 1950	Fasting	2272	1521	908	282	182	750		Jan. 1949	Fasting				438			
		2	1572	831	351	264	134	588		Feb. 1949	Fasting	4640	1200					
										June 1949	Fasting	2600	7200		223	140	380	

TL, Total Lipids; FA, Fatty Acids; NF, Neutral Fat; C, Total Cholesterol; CE, Cholesterol Esters; P, Phospholipids; T, Turbidity Index. All values are expressed as mg. per 100 cc. of serum except the turbidity index which is recorded as Moreton units.

TABLE 2.—*Lipid Ratios of Hyperlipemia Patients after Heparin*

Pt.	Date	Hour	$\frac{CE}{C}$	$\frac{C}{P}$	$\frac{FC}{P}$	Date	Hour	$\frac{CE}{C}$	$\frac{C}{P}$	$\frac{FC}{P}$
L. W.	1953	Fasting	65.5	1.16	0.400	1950	Fasting	64.8	0.367	0.119
		1	68.4	1.16	0.366		2	59.9	0.848	0.340
		2	62.5	1.14	0.426		4	59.1	0.952	0.390
		3	61.2	1.26	0.490					
		24	62.5	1.03	0.384					
E. I.	1953	Fasting	66.0	0.82	0.273	1950	Fasting	64.4	1.40	0.50
		1	66.6	0.952	0.317		4			
		2	73.8	0.858	0.225					
		3	45.8	1.05	0.568					
		24	76.6	0.815	0.190					
G. T.	Oct. 1953	Fasting	58.0	1.00	0.42	March 1953	Fasting	73.5	0.906	0.240
		1	63.8	0.994	0.362		1	68.6	0.958	0.301
		2	66.6	0.958	0.307		2	72.2	0.970	0.269
		3	60.8	0.912	0.358		3	74.8	0.892	0.225
		24	65.8	0.855	0.293		24	73.0	1.07	0.242
A. T.	1953	Fasting	80.7	1.28	0.246	1950	Fasting	64.2	2.20	0.788
		1	84.8	1.40	0.212					
		2	75.4	1.50	0.369					
		3	67.8	1.48	0.476					
		24	71.0	1.45	0.421					
H. O.	1953	Fasting	67.6	1.27	0.413	1950	Fasting	72.5	1.76	0.484
		1	65.9	1.20	0.408		2	53.1	1.91	0.899
		2	62.9	1.27	0.47		4	59.1	1.50	0.610
		3	72.6	1.46	0.40					
		24	68.0	1.03	0.331					
C. P.	1953	Fasting	70.1	1.60	0.478	1950	Fasting	72.1	1.25	0.348
		1	69.4	1.91	0.583		1	72.4	1.16	0.320
		2	70.9	1.96	0.572		2	71.2	0.71	0.207
		3	71.2	1.75	0.505		4	50.7	1.12	0.550
		24	70.7	1.49	0.437					
H. T.	Feb. 1950	Fasting	64.5	0.376	0.133	Jan. 1949	Fasting			
		2	50.8	0.449	0.222	Feb. 1949	Fasting			
						June 1949	Fasting	62.8	0.586	0.245

$\frac{CE}{C}$, Cholesterol Esters/Cholesterol; $\frac{C}{P}$, Cholesterol/Phospholipids; $\frac{FC}{P}$, Free Cholesterol/Phospholipids. All values are expressed as mg. per 100 cc. of serum, and phospholipids are expressed as lecithin or 25 × lipid phosphorus.

TL, Total Lipids; FA, Fatty Acids; NF, Neutral Fat; are expressed as mg. per 100 cc. of serum except the turbidity index which is recorded as Moreton units.

cations the skin temperatures before and after applications of heat to the lower extremities was measured under basal conditions in a special room kept at 66 F. The Rauh surface pyrometer was used. Diets used were not measured but gross reduction of cholesterol and/or fat was used. Glucose tolerance tests were done when indicated. The effect of heparin in essential hyperlipemia was tested by giving intravenous heparin to patients in the fasting state. The amount of heparin was 1 mg. per kilogram, and following this blood specimens were drawn at 1-hour, 2-hour, 3-hour and 24-hour intervals.

RESULTS

The blood chemistry figures (tables 1 and 2) demonstrate that for the period of observation, these patients with essential hyperlipemia showed no drastic change in their serum lipids. Improvement due to dietary restrictions or

TABLE 3.—*Serum Lipids in Controls after Heparin*

Pt.	Date	Hour	TL	FA	NF	C	CE	P	T
A. S.		Fasting	821	487	217	256	176	204	85
		1	790	458	208	254	154	203	66
		2	768	472	236	220	146	193	13
		3	739	428	183	236	158	190	17
		24	782	502	260	200	150	200	93
A. W.		Fasting	983	605	285	280	194	230	47
		1	868	502	191	282	214	220	6
		2	835	458	154	290	196	230	12
		3		590				182	13
		24	931	561	271	280	190	225	166
E. W.		Fasting	670	384	140	212	152	193	11
		1	659	325	60	245	158	221	8
		2	691	384	128	228	152	210	16
		3	706	413	156	207	159	213	28
		24	689	369	117	245	152	202	16

TL, Total Lipids; FA, Fatty Acids; NF, Neutral Fat; C, Total Cholesterol; CE, Cholesterol Ester; P, Phospholipids; T, Turbidity Index. All values are expressed as mg. per 100 cc. of serum except the turbidity index which is recorded as Moreton units.

TABLE 4.—*Ratios Controls after Heparin*

Pt.	Date	Hour	$\frac{CE}{C}$	$\frac{C}{P}$	$\frac{FC}{P}$
A. S.		Fasting	68.8	1.26	0.393
		1	60.6	1.25	0.493
		2	66.4	1.14	0.384
		3	67.0	1.24	0.410
		24	75.0	1.00	0.25
A. W.		Fasting	69.3	1.22	0.374
		1	72.4	1.28	0.309
		2	67.6	1.26	0.409
		3			
		24	67.1	1.25	0.40
E. W.		Fasting	71.8	1.10	0.31
		1	64.6	1.11	0.39
		2	66.7	1.09	0.36
		3	76.8	.97	0.22
		24	62	1.21	0.46

$\frac{CE}{C}$, Cholesterol Esters/Cholesterol; $\frac{C}{P}$, Cholesterol/Phospholipids; $\frac{FC}{P}$, Free Cholesterol/Phospholipids. All values are expressed as mg. per 100 cc. of serum and phospholipids are expressed as lecithin or 25 × lipid phosphorus.

weight reductions was only transient. This may be because the patients became careless in their eating habits, but it is more likely that a lipid escape phenomenon appeared since it occurred even if the patients were kept consistently at lower weight levels. The exception to this finding was patient G. T. who demonstrated dramatic return of serum levels to normal during combined dietary and heparin therapy (table 1). However, this individual had had the shortest period of observation, and it will be necessary to recheck these results within the next year before they can be considered more than a transitory phenomenon.

Heparin produced profound effects upon serum lipids in both healthy controls as well as in patients who had essential hyperlipemia (see tables 1, 2, 3 and 4). The maximum

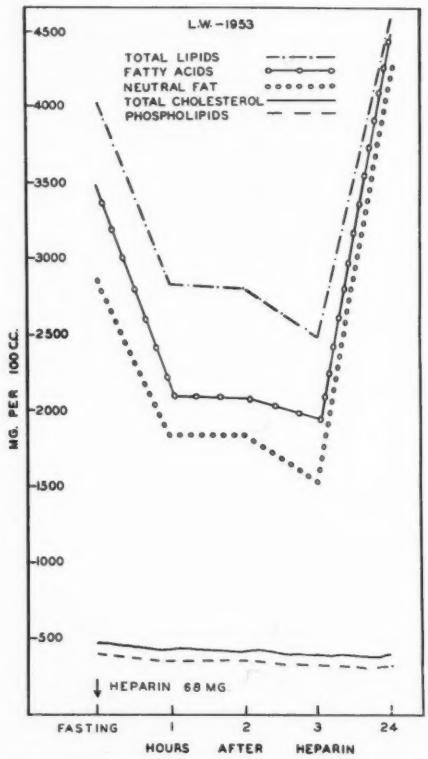

FIG. 1. Effect of heparin upon serum lipids in a patient with essential hyperlipemia.

egree of this effect occurred three to four hours after administration and serum levels returned to their previous levels within 24 hours (fig. 1). That this effect could be repeated after a six-month to three-year lapse of time was demonstrated by repeated tests in these patients (fig. 2). The lipid most drastically affected by heparin was neutral fat and accordingly changes occurred in the total lipids and fatty acids. With a rare exception (fig. 3) cholesterol and phospholipids showed a trend which was downward but statistically insignificant. This again is evidence that, exposed to dietary or pharmacologic factors, these two lipid components show less fluctuation than the more dynamic neutral fat.[11] Cholesterol and cholesterol ester values were determined by both the Bloor and the Schoenheimer-Sperry method, but, since the same trends are evident in the results, only the Bloor determinations are reported. When the relatively negligible response of serum cholesterol to heparin is contrasted to the drastic reorientation which heparin produces in the character of cholesterol distribution in the ultracentrifugal pattern there is striking evidence that the biochemical determination of serum lipids describes only a small part of the lipid state.[12] The turbidity index is a quantitative method of measuring the largest lipid particles, chylomicrons, which are composed primarily of neutral fat. This index measured in Moreton units showed approximately the same relative changes as chemical analyses of neutral fat (fig. 4). In recent years increasing importance has been attached to the ratio of

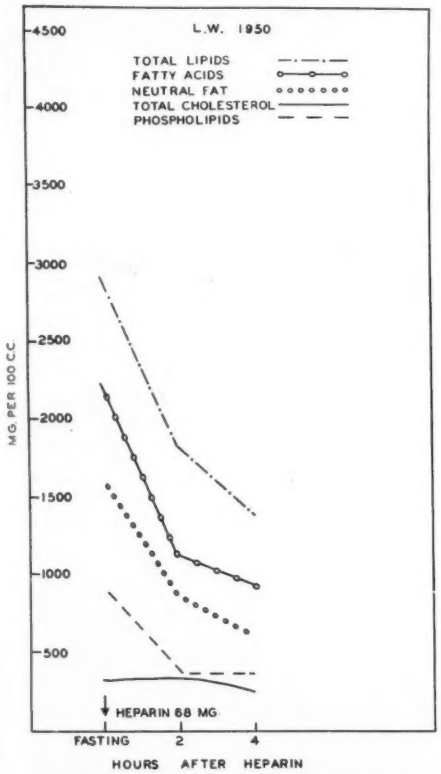

FIG. 2. Reproducibility of effect of heparin upon serum lipids in patient L. W. three years before test demonstrated in figure 1.

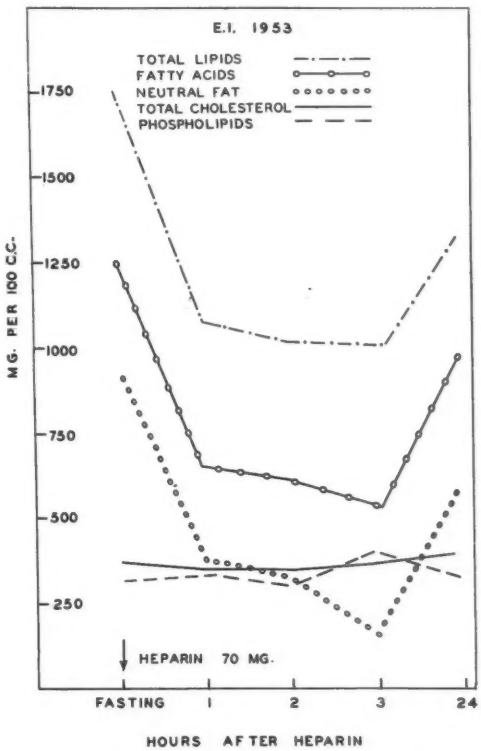

FIG. 3. Effect of heparin upon serum cholesterol and phospholipids in a patient with essential hyperlipemia. Like our other cases these values show no significant fall and even a slight rise in this instance.

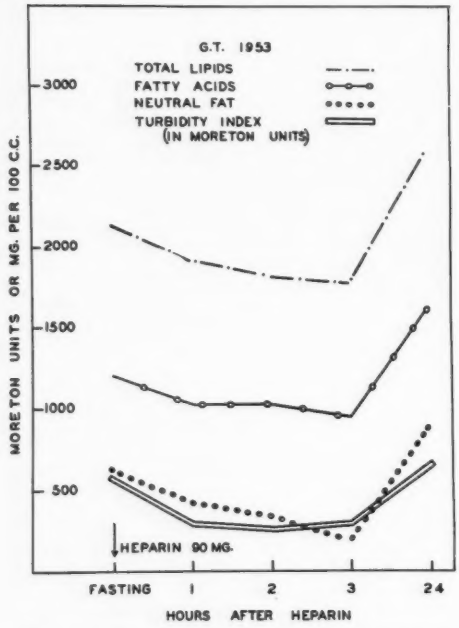

FIG. 4. Effect of heparin upon serum lipids in a patient with essential hyperlipemia demonstrating the fall in neutral fat and chylomicrons. (Turbidity Index expressed in Moreton units.)

cholesterol to phospholipids. More recently Jackson and Wilkinson[13] have minimized the reliability of this ratio and have instead recommended the use of the free cholesterol-phospholipid ratio. In tables 2 and 4 these two ratios as well as the cholesterol ester-cholesterol ratios are recorded for all patients and controls before and after heparin. Heparin produced neither marked nor consistent changes in these ratios. There is, in many cases, some indication of improvement in the cholesterol-phospholipid ratios, but it is unlikely that this is significant. A review of the fasting lipid ratios discloses no new concepts. These ratios often demonstrate what is felt to be a prognostically "bad" ratio, that is a high numerical ratio, but premature cardiovascular pathology is found in the presence of a "good" ratio, as for example in patient G. T. (table 2).

CASE HISTORIES

Case 1. G. T. is a 38 year old man who sought medical attention at the age of 35 because of xanthoma on his hands, elbows and knees. These lesions were painful when pressure was applied to them. The patient was put on a very moderately restricted low fat-low cholesterol diet, and this cleared up the hand lesions slowly during a period of one year. The patient has had symptoms which are characteristic of those of angina pectoris for the past one and one half years. In 1952 he had a prolonged episode of substernal pain. In March of 1953 the patient was put on a rigid weight reduction diet of 1000 calories and succeeded in losing 29 pounds in the next half year. During this period of weight reduction the lesions on the knees and the elbows began to disappear (fig. 5). In April 1953, heparin, 50 mg. intravenously, was given therapeutically twice weekly and, beginning in June 1953 the dosage was cut to 50 mg. once weekly and continued for five months. The patient's electrocardiogram (fig. 6) demonstrates an old anteroseptal myocardial infarction.

Case 2. E. I. is a 56 year old man, who has had symptoms of intermittent claudications for the past four years. His serum lipids are described in tables 1 and 2 and in figure 3. The patient had a markedly abnormal temperature response as manifested by skin temperature changes demonstrated in figure 7. The temperature curve in the bottom of the figure shows marked improvement following a regimen of weight reduction.

Case 3. Patient A. T. is a 35 year old man who has xanthomas. For the past four years the patient

FIG. 5. Elbow of patient G. T. demonstrating xanthoma.

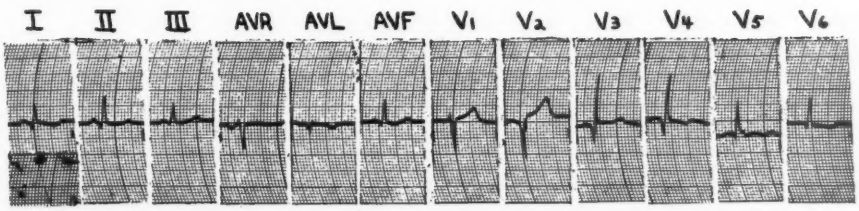

FIG. 6. Electrocardiograms of patient G. T., 1953 showing the pattern of old anteroseptal myocardial infarction.

has had repeated episodes of substernal pain which are suggestive of angina pectoris. The patient has not been able to work because of this distress. The only objective evidence of heart disease is a distinctively abnormal ballistocardiogram which is pictured in figure 8 in a somewhat improved state. The patient's blood lipid analyses are demonstrated in tables 1 and 2.

DISCUSSION

The serum hypercholesterolemia so frequently found in essential hyperlipemia is considered to be due neither to increased production nor to increased utilization or transportation of fat depots.[2] The hypercholesterolemia may be entirely secondary to the greater carrying capacity of the elevated level of serum neutral fat. Whatever the mechanism of this hypercholesterolemia is, it is our fervent belief that these patients must be watched for signs of premature atherosclerosis. Four of the seven patients described in this manuscript manifested both signs or symptoms of premature atherosclerotic involvement of the coronary or peripheral vascular tree (table 5). Serum lipid studies in these subjects possess, therefore, an urgent clinical appeal.

That essential hyperlipemia may be hereditary has been commented upon before. Our data give further credence to this concept, for the sister of patient L. W. demonstrates the same abnormal pattern of serum lipids that he shows (tables 1 and 6). The blood serum values of the mother of patient G. T. are distinctly those of hyperlipemia (table 6), and

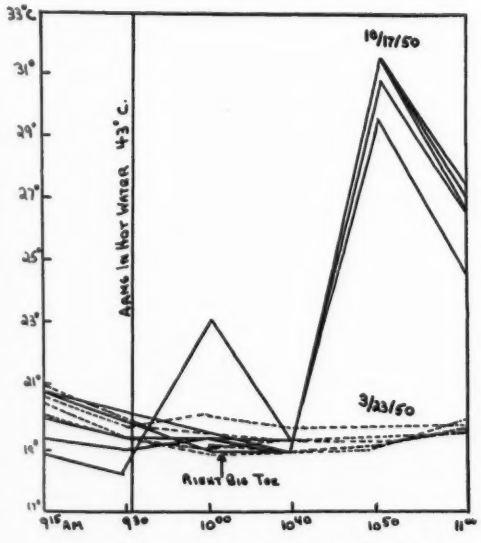

FIG. 7. Skin temperatures of the right foot following immersion of the arms in hot water (43 C.) in patient E. I. Each line represents one toe, the dotted lines on 3/23/50 and the solid lines on 10/17/50. The arrow points to the time interval on 3/23/50 when the right big toe showed a bluish discoloration. Such discoloration did not occur on 10/17/50.

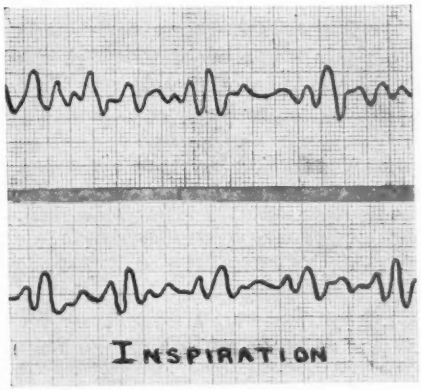

FIG. 8. Ballistocardiogram of patient A. T. During inspiratory breath-holding amplitude decreases and most complexes are not identified. During expiration the amplitude increases to a normal level with well-formed, definitive complexes seen.

TABLE 5.—*Clinical Status of Seven Patients with Essential Hyperlipemia*

Patient	Age	Symptoms	Objective Findings	Signs and Symptoms	Therapy	Duration of Observation (years)
H. O. Male	46	(1) Intermittent claudications (2) Angina pectoris	(1) Xanthoma (2) Abnormal skin temp. response. Right leg	8 years	Low fat, low chol. diet Wt. loss—18 lbs.	3
E. I. Male	56	Intermittent claudications	Abnormal skin temp. response. Right leg	6 years	Low fat, low chol. diet Wt. loss—16 lbs.	3
H. T. Female	46	None	None (i.e. other than serum lipids)	Known hyperlipemia 8 years	Low fat diet	1
R. P. Male	61	None	Xanthoma	5 years	Low fat, low chol. diet	3
L. W. Male	41	None	Lipemia retinalis	5 years	Low fat, low chol. diet	3
A. T. Male	35	Angina pectoris?	Markedly abnormal ballistocardiogram	5 years	Low fat, low chol. diet	4
G. T. Male	38	Angina pectoris One episode of prolonged chest pain	Xanthoma Myocardial infarct pattern electrocardiogram	Skin lesions 3 years. Angina pectoris 1½ years	Low caloric diet Wt. loss 30 lbs. Heparin	1

it is instructive to note that the serum lipid pattern of the father of G. T. is entirely normal. The mother's hyperlipemia may, however, be secondary rather than essential because unlike all other subjects in this series (by definition) she has diabetes mellitus. Another comparable mother-male child relationship was discovered (patient L. W.), and we have begun further investigation of possible subclinical relationships between these fascinating metabolic diseases.

TABLE 6.—*Fasting Serum Lipid Values of Close Relatives of Two of Our Patients with Essential Hyperlipemia. Sister of L. W. Has Essential Hyperlipemia, Mother of G. T. Has Secondary Hyperlipemia*

Subject	TL	FA	NF	C	CE	P	Turbidity
Sister of L. W....	4073	3365	2955	480	292	400	Lipemic
Mother of G. T....	1257	700	259	403	218	418	Lipemic

TL, Total Lipids; FA, Fatty Acids; NF, Neutral Fat; C, Total Cholesterol; CE, Cholesterol Esters; P, Phospholipids; T, Turbidity Index. All values are expressed as mg. per 100 cc. of serum except the turbidity index which is recorded as Moreton units.

Intravenous heparin produced profound changes in the sera of our patients, but we feel that it is impossible at this time to state that heparin should be considered to be a therapeutic agent in essential hyperlipemia. Eventually we must answer the question, what happens to the lipids in the sera that heparin clears? The Danish investigators[14] suggest that sulfur-containing compounds such as heparin predispose to a release or precipitation of lipids in blood vessel walls. The spectacular lipid response of patient G. T. to weekly and biweekly therapeutic injections of heparin cannot be denied, but the role of weight reduction which occurred concomitantly in this patient must be evaluated before the role of heparin can be decided upon.

CONCLUSIONS

Seven patients with essential hyperlipemia, with an average age of 46 years, were observed for an average period of two and one-

half years. Four of these subjects manifested objective and subjective evidence of premature atherosclerosis. Repeated serum lipid analyses in these patients and in normal controls after specific dietary or total caloric restrictions revealed a relatively static blood picture when viewed in terms of years rather than months.

Intravenous heparin produced dramatic though transient lowering of total lipids, but this was predominantly due to its action upon neutral fats since cholesterol and phospholipids showed only minimal changes. This characteristic of heparin could be demonstrated repeatedly.

The prolonged use of heparin as a therapeutic agent was studied, and though no certain effect can be attributed to this therapy, further study in this direction is warranted.

The turbidity index described in Moreton units is a means of determining quantitatively the changes in chylomicrons, but the biochemical determination of serum neutral fat permits the observation of the same trends.

A dispersing property of heparin could produce the changes in the ultracentrifugal and chylomicron values but there is no explanation at this time for the absolute decrease in neutral fat following heparin administration.

Heparin produced no consistent effect upon the cholesterol-phospholipid, free cholesterol-phospholipid or cholesterol esters–cholesterol ratios.

Our control subjects showed no significant differences in their lipid responses to heparin, though of course the degree of these changes was comparatively smaller.

Sumario Español

Siete pacientes con hiperlipemia esencial, con un promedio de edad de 46 años, fueron observados por un promedio de dos años y medio. Cuatro de estos sujetos manifestaron evidencia objetiva y subjetiva de ateroesclerosis prematura. Repetidos análisis del suero para lípidos en estos pacientes y en controles normales luego de restricciones específicas en cuanto a la dieta y total de calorías, revelaron un cuadro relativamente estático cuando se visualizó en término de años en lugar de meses.

La heparina intravenosa produjo un decremento dramático transiente en el total de lípidos, pero esto fué predominantemente debido a la acción en la grasas neutrales porqué el colesterol y las fosfolipinas mostraron solamente cambios mínimos. Esta característica de la heparina se pudo demostrar repetidamente.

El uso prolongado de heparina como un agente terapeútico se estudio y aunque ningún efecto cierto puede ser atribuido a esta terapia, más investigacion en esta dirección está justificada.

El índice de turbieza descrito en unidades Moreton es un medio de determinar cuantitativamente los cambios en quilomicrones, pero la determinación bioquímica de la grasa neutral del suero permite la observación de las mismas tendencias.

La propiedad de dispersar de la heparina puede producir los cambios en los valores de la ultracentrifuga y quilomicrones pero no existe explicación en el presente para el decremento en grasa neutral que acompaña a la administración de la heparina.

La heparina no produjo un efecto consistente en las proporciones de colesterol-fosfolipina, colesterol libre-fosfolipina o esteres de colesterol-colesterol.

Nuestros sujetos controles no mostraron diferencias significativas en sus respuestas lípidas a la heparina aunque naturalmente el grado de estos cambios fué comparativamente más pequeño.

Acknowledgments

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A Comparison of the Cerebral Hemodynamic Response to Aramine and Norepinephrine in the Normotensive and the Hypotensive Subject

By JOHN H. MOYER, M.D., GEORGE MORRIS, M.D., AND HARVEY SNYDER, M.D.
WITH THE TECHNICAL ASSISTANCE OF C. POLK SMITH

Previous observations have demonstrated a depression in cerebral blood flow during controlled hypotension with ganglionic blocking agents. Cerebral blood flow is also decreased when normotensive individuals are made hypertensive by the administration of vasopressor agents. The opposite response is observed when hypotensive individuals are made normotensive by the administration of these same agents, in which circumstance cerebral blood flow is increased.

EXPERIMENTAL work on the cerebral circulation in laboratory animals has indicated that the volume of blood flowing through the brain parallels the systemic blood pressure.[1] Observations which were made following the administration of dihydroergocornine to normotensive subjects[2] showed that cerebral blood flow is not altered following minor reductions in blood pressure. However, when the blood pressure is reduced to moderate or marked hypotensive levels, the cerebral blood flow decreases.[3] When norepinephrine is infused intravenously into normotensive subjects the cerebral blood flow decreases as the blood pressure rises[4, 5] to hypertensive levels, probably indicative of preferential cerebral vasoconstriction. It has been suggested that this latter response might have a harmful effect on the brain by superimposing additional cerebral vasoconstriction when such vasopressor agents as norepinephrine are used for the treatment of hypotensive states.[4] The purpose of the current report was to study the effect of a synthetic vasopressor amine (Aramine) on the cerebral circulation in the normotensive individual and to compare this response with that of norepinephrine. Additional comparisons were made on the response of normotensive subjects who have been made hypertensive by giving a vasopressor agent, as compared with the response when the blood pressure was only returned to control levels in patients who were previously made hypotensive by a ganglionic blocking agent.

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Aramine, levo 1-(m-hydroxphenyl)-2-amino-1-propanol, supplied through the courtesy of Sharp and Dohme, Inc.

Norepinephrine supplied through the courtesy of Winthrop-Stearns, Inc.

METHODS

Cerebral hemodynamic studies were made on 22 normal subjects. The patients were divided into two groups. There were 11 patients in group 1, all of whom were normotensive. Seven of them received Aramine and four received norepinephrine. Only four patients received norepinephrine because our observations merely confirmed the previously reported observations of others,[4, 5] which indicated that cerebral blood flow was slightly depressed by this agent when administered to normotensive subjects. Therefore, further studies did not appear to be indicated. Cerebral blood flow was determined by the nitrous oxide method.[6] Analytic technics and procedures used have previously been described.[7] After suitable control observations, the vasopressor agent was administered by continuous intravenous infusion at a rate adequate to increase the blood pressure about 30 to 40 per cent. The concentration of Aramine was 50 mg. per liter in normal saline. The concentration of norepinephrine was 4 mg. per liter. After the blood pressure was stabilized at the hypertensive levels for 10 to 15 minutes the cerebral blood flow determinations were again repeated.

Control observations on the 11 patients in group 2 were made in a similar manner to the control

TABLE 1.—*The Effect of Blood Pressure Elevation with Aramine on Cerebral Hemodynamics*

Pt.	Pulse Rate		Mean Bl. Press.†		Cerebral Blood Flow ml./100 Gm./min.		Cerebrovasc. Resist.*		Cerebral O_2 Uptake‡		Hemat.		Auscult. Bl. Press. Syst.		Auscult. Bl. Press. Diast.		Respiratory Rate	
	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
Response to Aramine																		
B.W.	96	64	82	112	47	37	1.7	3.0	3.1	1.7	46	46	110	140	72	100	24	24
B.S.	102	64	75	116	69	62	1.1	1.9	4.1	5.0	38	39	90	154	58	88	18	16
V.A.	76	62	88	130	46	56	1.9	2.3	3.7	4.4	36	36	110	190	80	130	28	14
C.D.	92	76	96	135	70	46	1.4	2.9	2.4	1.6	36	36	120	170	80	122	—	—
C.B.	88	64	95	118	48	42	2.0	2.8	3.5	2.7	52	52	120	160	80	85	20	18
J.T.	86	70	88	122	54	48	1.6	2.5	3.8	3.3	44	44	114	148	80	110	15	14
E.L.	108	64	90	110	74	78	1.2	1.4	3.2	3.4	32	32	110	142	78	95	20	23
Mean	93	66	88	120	58	53	1.6	2.4	3.4	3.2	41	41	111	158	75	104	21	18
Stat. sig.	p less than 0.01				$p < 0.5$		$p < 0.10$		$p < 0.5$		$p < 0.5$							
Mean % of control		71		136		91		150		94		100		142		139		86
Response to Norepinephrine																		
S.J.	86	68	101	132	61	56	1.7	2.4	4.0	4.0	32	32	141	184	80	104	20	18
E.T.	78	56	85	123	57	51	1.5	2.4	3.7	3.4	36	36	128	187	72	93	16	15
D.A.	100	78	90	117	46	41	2.0	2.9	2.6	2.6	46	47	131	162	78	88	18	16
E.R.	88	60	98	125	62	50	1.6	2.5	4.6	3.9	35	35	128	185	79	90	17	17
Mean	88	66	94	124	57	50	1.7	2.6	3.7	3.5	37	38	132	180	77	94	18	17
Stat. sig.	p less than 0.01				$p <$ 0.3		$p <$ 0.02		$p < 0.5$		$p < 0.5$							
Mean % of control		75		132		88		153		95		103		136		122		94
Stat. sig. combined observations on Aramine & norepinephrine	p less than 0.01				$p <$ 0.3		$p <0.01$		$p < 0.5$									

† Mean Blood Pressure—direct arterial manometry.

* Cerebrovascular Resistance = $\frac{\text{Mean Blood Pressure.}}{\text{Cerebral Blood Flow}}$

‡ Cerebral Oxygen Uptake per 100 Gm./brain/minute.

C, Control; D, After blood pressure elevation; Stat. Sig., Statistical significance.

observations on the patients in group 1. Then the blood pressure was reduced by a continuous infusion of one of the ganglionic blocking agents (hexamethonium, Pendiomide* or Arfonad†) until maximum reduction in blood pressure was obtained or the mean blood pressure was approximately 50 mm. Hg.[3] The average rate of infusion of Pendiomide was 5 mg. per minute, of hexamethonium, 4 mg. per minute, and of Arfonad, 7 mg. per min-

* Pendiomide (pentamethyl-diethyl-3-azo-pentane-1,5-diammoniumdibromide) furnished through the courtesy of Ciba Pharmaceuticals, Inc.

† Arfonad (d-3,4(1′,3′-dibenzyl-2′-keto-imidazolido)-1,2-trimethylene thiophanium d-camphor sulfonate) furnished through the courtesy of Hoffmann-LaRoche, Inc.

TABLE 2.—*The Effect of Blood Pressure Elevation with Aramine on Cerebral Blood Constituents*

Pt.	Arterial O_2 Vol. %		Venous O_2 Vol. %		A-V O_2 Difference Vol. %		Art. CO_2 Vol. %		Ven. CO_2 Vol. %		Art. P CO_2 mm./Hg		Ven. P CO_2 mm./Hg		Jugular Press.	
	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
Response to Aramine																
B.W.	17.6	16.4	11.0	11.9	6.6	4.5	35.2	34.2	40.6	39.3	41	38	47	45	14.5	14.5
B.S.	15.1	14.9	9.2	6.8	5.9	8.1	40.6	37.4	45.9	45.6	40	39	46	43	7.7	9.1
V.A.	15.9	15.6	7.8	7.8	8.1	7.8	42.4	37.2	48.6	45.4	31	28	58	49	10.6	9.0
C.D.	11.4	12.1	8.0	8.7	3.4	3.4	48.5	47.6	51.3	52.1	41	50	54	64	7.5	7.3
C.B.	18.9	17.7	11.7	11.2	7.2	6.5	37.6	46.2	43.6	52.6	41	41	48	50	11.2	10.0
J.T.	19.2	18.8	12.1	11.9	7.1	6.9	45.1	46.1	53.0	54.2	39	39	51	50	—	—
E.L.	10.5	10.3	6.2	6.0	4.3	4.3	53.1	52.3	57.7	56.1	38	39	46	46	10.0	12.0
Mean	15.5	15.1*	9.4	9.2*	6.1	5.9*	43.2	43.0*	48.7	49.3*	39	39*	50	50*	10.2	10.3*
Mean % of control		97		98		97		100		101		100		100		101
Response to Norepinephrine																
S.J.	14.4	14.6	7.8	7.5	6.6	7.1	46.2	41.9	51.8	49.1	44	39	51	48	—	—
E.T.	13.5	13.7	7.0	7.0	6.5	6.7	41.2	38.6	46.8	45.2	40	37	49	49	—	—
D.A.	17.8	17.1	12.1	10.8	5.7	6.3	49.8	46.2	56.6	52.7	44	40	51	48	—	—
E.R.	15.9	15.8	8.5	8.1	7.4	7.7	40.1	39.1	46.9	46.1	40	41	48	49	—	—
Mean	15.4	15.3	8.9	8.4	6.6	7.0	44.3	41.5	50.5	48.3*	42	39*	50	49*	—	—
Mean % of control		99		94		106		94		96		93		98		

* Not statistically significant.

ute. Since the blocking agents were administered for at least 30 minutes, the amount of drug infused over this period of time should be adequate to block autonomic ganglia, as estimated by vagal ganglionic blockade, if this response in man is of the same order of sensitivity as it is in the dog. After the blood pressure was maintained at hypotensive ranges for 15 to 20 minutes, observations on cerebral blood flow were again made. The infusion of the ganglionic blocking drug was then continued and norepinephrine or Aramine was infused as rapidly as necessary to return the blood pressure to or above the control observations. After the blood pressure was restabilized at this level, the cerebral blood flow was again determined and the results compared with those obtained on the patients in group 1 in whom the same vasopressor agents were administered to normotensive subjects whose blood pressures were subsequently increased to hypertensive levels.‡

‡ The absolute increase in blood pressure (mm. Hg) after the vasopressor agent was somewhat greater in the patients in group 2 as compared with group 1 and the percentile increase was considerably larger.

RESULTS

The mean arterial blood pressure was increased about 36 per cent on the average for the group of patients receiving Aramine alone. This was due to a rise in both systolic and diastolic pressure and was associated with a sharp increase in cerebrovascular resistance which was statistically significant (p less than 0.10). The response to norepinephrine was similar (p less than 0.02). When the observations on the response to Aramine and norepinephrine were combined the increase in cerebrovascular resistance was highly significant (p less than 0.01). There was frequently a reduction in cerebral blood flow during the administration of Aramine quite similar to that seen in patients receiving norepinephrine (4) (table 1), although the change was not statistically significant for the group. The cerebral oxygen consumption ($CMRO_2$) showed considerable variation but this did not appear

TABLE 3.—*Observations on Cerebral Oxygen Metabolism and Cerebral Hemodynamic Response to Blood Pressure Elevation with Vasopressor Agents Following Initial Hypotension Due to Ganglionic Blockade*

Pt.	Ganglionic Blocking Agent	Vasopressor Agent	Mean Bl. Press. (mm. Hg)			Cerebral Blood Flow			Cerebrovasc.† Resist.			Cerebral O_2† Consump.			A-V O_2 Diff.		
			C	D	V	C	D	V	C	D	V	C	D	V	C	D	V
1.	Arfonad	Norepinephrine	96	52	120	40	25	36	2.4	2.1	3.3	2.6	2.0	2.4	6.4	8.0	6.6
2.*	Arfonad	Norepinephrine	96	75	105	58	38	51	1.7	2.0	2.1	2.8	2.9	3.2	4.8	7.7	6.3
3.	Arfonad	Norepinephrine	110	58	110	48	35	38	2.3	1.7	2.9	2.5	2.7	2.9	5.2	7.7	7.5
4.	Arfonad	Norepinephrine	94	44	110	41	25	35	2.3	1.8	3.1	2.9	2.6	2.6	7.0	10.2	7.5
5.	Hexamethonium	Aramine	108	61	120	52	44	56	2.1	1.4	2.1	4.1	3.7	3.8	7.9	8.4	6.7
6.	Hexamethonium	Aramine	98	68	118	49	36	64	2.0	1.9	1.8	2.6	2.2	2.9	5.2	6.2	4.5
7.	Hexamethonium	Aramine	104	61	105	75	36	65	1.4	1.7	1.6	4.1	3.3	4.0	5.4	9.1	6.1
8.	Hexamethonium	Norepinephrine	100	80	140	69	58	65	1.5	1.4	2.2	3.0	2.6	3.4	4.3	4.5	5.2
9.	Hexamethonium	Norepinephrine	96	54	118	56	40	50	1.7	1.4	2.4	2.8	3.1	2.5	5.0	7.8	5.0
10.	Hexamethonium	Norepinephrine	100	53	96	54	34	42	1.9	1.6	2.3	3.6	2.9	3.0	6.7	8.4	7.2
11.‡	Pendiomide	Norepinephrine	111	66	110	49	51	53	2.3	1.2	2.1	2.9	3.2	3.0	6.0	6.2	5.7
Mean			101	61	114	54	38	50	2.0	1.7	2.4	3.1	2.8	3.1	5.8	7.7	6.2

† See table 1 for methods of measurement.

* When blood pressure increased from 110 to 145 the cerebral blood flow decreased to 38 and the arterial-venous oxygen increased to 8.4 volume per cent.

‡ When blood pressure increased from 110 to 155, the cerebral blood flow decreased to 49 and the arterial-venous oxygen increased from 5.7 to 6.3.

C = control observations; D = observations after blood pressure reduction with ganglionic blocking agent; V = observations after blood pressure elevation with vasopressor agent.

to be affected in any consistent manner. These variations probably reflect unstable cerebral hemodynamics.

The administration of Aramine was not associated with any significant alterations in oxygen or carbon dioxide content of the blood flowing to or from the brain. There were no alterations in the partial pressure of arterial carbon dioxide. Although there was some variation in the extraction of oxygen from the blood as it passed through the brain, this too was inconstant. In the case of norepinephrine, there was a small but rather constant increase in the extraction of oxygen (jugular blood), probably a reflection of a slightly greater reduction in cerebral blood flow. These responses to norepinephrine, which have previously been reported,[4, 5] occurred irrespective of directional alterations in arterial partial pressures of carbon dioxide (p CO_2). This indicates that the reduction in cerebral blood flow is due to the vasoconstrictor effect of the drug rather than due to hyperventilation and a reduction in arterial partial pressure of carbon dioxide.

When the blood pressure was reduced significantly with any of the ganglionic blocking agents, the cerebral blood flow decreased. The extraction of oxygen from the blood was increased and thus, for the most part, cerebral anoxia was prevented. However, in several instances when the pressure was markedly reduced, this compensation was inadequate and the oxygen uptake ($CMRO_2$) decreased. The cerebral hemodynamic response to raising the blood pressure from hypotensive levels to normotensive ones was quite consistent. As the blood pressure rose, the cerebral blood flow returned to or approached control levels and the cerebral oxygen consumption ($CMRO_2$) if previously depressed also returned towards the control value. As the cerebral blood flow increased the compensatory increase in arteriovenous oxygen difference, which previously existed, now decreased.

DISCUSSION

It appears that in normotensive subjects the cerebral vascular response to Aramine is at least qualitatively similar to the response to norepinephrine. As the blood pressure is increased to hypertensive ranges these vasoconstrictor agents have a direct effect on the

cerebral vessels which is somewhat greater than on the over-all circulatory bed. As a result, the cerebral blood flow is slightly decreased in some instances. A different set of circumstances exist when the blood pressure is reduced to hypotensive ranges. Since the cerebral circulation is probably not under the regulation of the autonomic nervous system,[1] the cerebral circulation will be more dependent (passively) on systemic blood pressure and local cerebral tissue factors which are responsible for maintaining cerebrovascular resistance than is true of the general circulation. Therefore, when the blood pressure is moderately reduced, the cerebral blood flow also decreases unless local tissue factors act in such a manner as to produce vasodilatation (active or passive) and thus return the blood flow to the control levels. The net result will depend on the intensity of the individual opposing forces.

When the systemic blood pressure is reduced with ganglionic blocking agents, cerebral blood flow is depressed. This is quickly reversed when the blood pressure is returned to control levels with norepinephrine or Aramine. Figures 1 and 2 are typical responses. Presumably, the same type of response would be observed if the blood pressure were reduced by hemorrhage

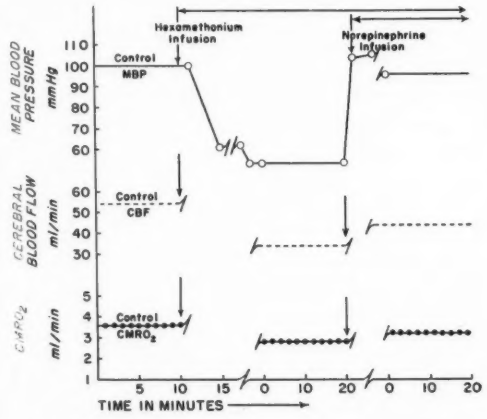

FIG. 1. Associated with the blood pressure reduction, cerebral blood flow is moderately reduced and cerebral oxygen uptake ($CMRO_2$) is slightly reduced. When the blood pressure is increased with norepinephrine cerebral blood flow and $CMRO_2$ return toward the control levels. This is a rather typical cerebral hemodynamic response.

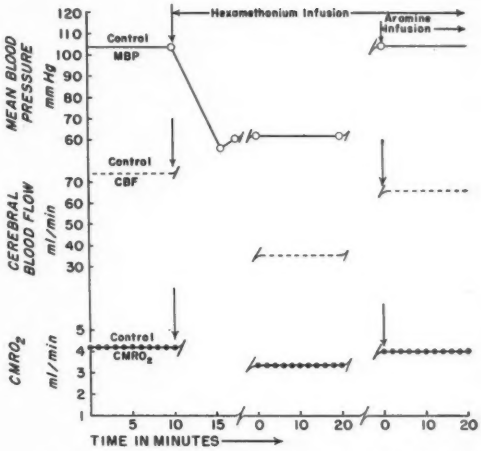

FIG. 2. When the blood pressure was reduced with hexamethonium the cerebral blood flow was markedly depressed and cerebral oxygen uptake ($CMRO_2$) moderately so. Following an infusion of Aramine the blood pressure was increased. This was associated with a return of cerebral blood flow and $CMRO_2$ toward the control levels. There was essentially no difference between the response to norepinephrine (fig. 1) and the response to Aramine.

or shock due to other causes. Under these circumstances cerebral blood flow would probably be depressed. Administering a vasopressor agent and thus raising the blood pressure towards normotensive levels could then be expected to increase cerebral blood flow towards normal. This suggests that improvement in the cerebral circulation can be expected to follow the use of vasopressor agents when used to increase the blood pressure from hypotensive levels to normotensive ones during the treatment of hypotensive states resulting from numerous causes. This is in direct contrast to the response when these vasopressor agents are used to raise the blood pressure from normotensive levels to hypertensive ones.

SUMMARY AND CONCLUSIONS

1. Observations were made on the cerebral hemodynamic response to raising the blood pressure from normotensive levels to hypertensive ones through the use of a continuous infusion of Aramine or norepinephrine. As the blood pressure increased, cerebral blood flow decreased.

2. When the blood pressure was reduced by the use of ganglionic blocking agents (Arfonad, hexamethonium, or Pendiomide), cerebral blood flow was depressed. The extent of depression was usually greatest in the patients with marked hypotension. As the cerebral blood flow decreased, cerebral oxygen consumption was partially maintained due to a more complete extraction of oxygen from the blood flowing through the brain. However, compensation was inadequate and cerebral anoxia was observed in several of the patients who developed very marked hypotension. When the blood pressure was returned from hypotensive levels to normotensive ranges by administering Aramine or norepinephrine, the cerebral blood flow actually increased. This response was in sharp contrast to raising the pressure from normotensive to hypertensive levels.

3. These observations suggest that when vasopressor agents are used for the treatment of severe hypotension, the therapist can expect an increase in cerebral blood flow and improvement of cerebral function.

Sumario Español

1. Observaciones fueron hechas en la respuesta de la hemodinámica cerebral al incremento de la presión arterial de niveles normotensos a niveles hipertensos mediante el uso de una infusión contínua de Aramine o norepinefrina. A medida que la presión aumentó la circulación cerebral disminuyó.

2. Cuando la presión arterial fué reducida con el uso de agentes bloqueadores gangliónicos (Arfonad, hexamethonium o Pendiomide), la circulación cerebral disminuyó. La extensión del decremento fué usualmente mayor en los pacientes con marcada hipotensión. A medida que la circulación cerebral disminuyó, el consumo de oxígeno cerebral fué parcialmente mantenido debido a una más completa extracción de oxígeno de la circulación sanguínea cerebral. Sinembargo, la compensación fue inadecuada y anoxia cerebral se observó en diferentes pacientes que desarrollaron muy marcada hipotensión. Cuando la presión arterial retornó de niveles hipotensos a niveles normotensos mediante la administración de Aramine o norepinefrina, la circulación cerebral actualmente aumentó. Esta respuesta estuvo en contraste agudo con la obtenida cuando se aumentó la presión de niveles normotensos a hipertensos.

3. Estas observaciones sugieren que cuando agentes vasopresores se usan para el tratamiento de la hipotension marcada, el terapeuta puede esperar un incremento en la circulación cerebral y una mejoría en la función cerebral.

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The Relation between Blood Organic Acid Soluble Phosphate Fractions, Citric Acid, Protein Fractions, and Lipid Fractions in Atherosclerotic Heart Diseases and in Lipemias

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Blood organic acid soluble phosphate fractions and serum citric acid determinations were performed on 39 carefully chosen cases of atherosclerosis, in order to determine whether any abnormalities might be detected in the oxidative phosphorylation of glucose or in the Krebs tricarboxylic acid cycle, respectively. No differences were observed between a series of normal individuals and atherosclerotic patients. Likewise, serum protein fractionations determined chemically revealed no differences. Only the serum lipid fractions, the total lipids and total cholesterol in particular, were elevated in 60 per cent of the atherosclerotic patients as compared with the normal subjects.

In the recent past a number of investigators have presented evidence that lipid metabolism plays a role in the pathogenesis of atherosclerosis. Some investigators[1, 2] have claimed that the deposition of cholesterol in the arterial walls may depend upon the concentration of total cholesterol in the blood. Others[3, 4] have stated that the level of plasma cholesterol is not the determining factor, and that only those individuals who have a high cholesterol–lipid phosphorus ratio tend to deposit cholesterol in the arteries. Other investigators[5, 6] have demonstrated that in atherosclerotics the S_f 12–20 lipoproteins play a more important role than the cholesterol or the cholesterol–lipid phosphorus ratio.

It was considered that atherosclerotics might reveal some impairment in carbohydrate metabolism which could be detected by a study of the blood organic acid soluble phosphate fractions and the serum citric acid, and which might be correlated with the lipid abnormalities observed. The former are indicative of the oxidative phosphorylation of glucose, while the latter is a product of the Krebs cycle which accomplishes the aerobic oxidation of pyruvic acid (an end product of the anaerobic breakdown of glucose) and of intermediates in lipid and protein metabolism. This study was initiated in an attempt to investigate the possible existence of any such relationship in atherosclerosis. In addition, the routine plasma lipids and the serum protein fractions were performed.

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Methods

For this study a group of normal adults who had no organic disturbance and who were under 55 years of age, and a group of diagnosed atherosclerotic subjects were chosen and the following blood chemistry determinations performed.

(1) Organic acid soluble phosphate fractions including adenosine triphosphate phosphorus, diphosphoglyceric acid phosphorus, hexose phosphate phosphorus, total organic acid soluble phosphorus, and inorganic phosphorus in the blood.[7, 8] (2) Serum citric acid.[9] (3) Serum protein fractions.[10] (4) Plasma lipid fractions including total and free cholesterol, lipid phosphorus, and total lipids.[11–14]

In the clinical diagnosis of atherosclerosis, the following criteria were employed.

(1) In order to attempt to restrict this study to atherosclerotics, the patient had to be under 55 years of age. (2) Atherosclerotics having diabetes or familial xanthomatosis were not included. (3) Those with an antecedent history of congenital or acquired

heart disease or of hypertensive vascular disease were excluded from the study. (4) The patient must have had a proven coronary thrombosis with myocardial infarction or anginal syndrome with myocardial ischemia.

The above criteria were checked wherever possible by postmortem findings. However in only two patients were necropsies obtained.

Results and Discussion

In table 1 are listed a comparison of the results obtained in the normal individuals and the atherosclerotic patients. From this table the following observations may be made.

The blood organic acid soluble phosphate fractions and the serum citric acid levels reveal no significant differences between the normals and the atherosclerotics. Therefore, if any abnormalities in carbohydrate metabolism exist, the chemical methods employed in this study are incapable of detecting them. Thus we are unable to demonstrate any relation between the blood organic acid soluble phosphate fractions, the serum citric acid, and the plasma lipid fractions in the atherosclerotic.

The serum protein fractions likewise revealed no differences. Baker and Merivale[5] who utilized the same procedure for fractionating serum proteins as was used here, observed that the method is not reliable for detecting slight alterations in levels of alpha and beta globulins. It is intended to further investigate the serum proteins by paper electrophoresis.

The only abnormalities observed lie in the plasma lipids. In this study the normal range for the total lipids is considered to be 375 to 800 mg. per 100 cc and for the total cholesterol 140 to 300 mg. per 100 cc. On this basis considerable overlapping occurs; but on the whole, the mean for the atherosclerotic is considerably higher than that for the normal. The increase in free cholesterol parallels the rise in total cholesterol as evidenced by the

Table 1.—*A Comparison of the Blood Chemistry Results Obtained for the Normal Individuals and the Atherosclerotic Cases*

Determination	Normals			Atherosclerotics		
	No. of cases	Range	Mean	No. of cases	Range	Mean
Inorganic phosphorus (mg. %)	50	3.9–6.6	4.9 ± 0.7	37	3.0–6.3	5.0 ± 0.8
Adenosine triphosphate phosphorus (mg. %)	50	3.1–6.9	5.0 ± 0.6	37	3.2–7.0	4.8 ± 0.7
Adenylic acid P & hexose phosphate P (mg. %)	50	3.5–9.4	7.2 ± 1.0	37	4.7–9.3	7.4 ± 0.8
Diphosphoglyceric acid phosphorus (mg. %)	50	6.3–14.0	10.5 ± 1.3	37	6.2–13.0	10.5 ± 1.4
Total organic acid soluble P (mg. %)	50	21.8–33.3	27.5 ± 2.3	37	21.5–32.4	28.0 ± 1.9
Citric acid (mg. %)	38	1.1–3.0	1.6 ± 0.3	32	0.9–3.0	1.5 ± 0.4
Total lipids (mg. %)	47	373–785	580 ± 93	39	573–1240	873 ± 154
Total cholesterol (mg. %)	50	141–300	207 ± 29	39	153–405	303 ± 51
Free cholesterol (mg. %)	48	30.5–76.3	53.7 ± 9.0	38	44.5–116	78.6 ± 15.7
% Free cholesterol	48	17.7–30.9	26.0 ± 2.8	38	20.6–34.5	27.1 ± 2.9
Lipid phosphorus (mg. %)	50	6.3–13.6	9.3 ± 1.5	38	8.7–15.2	11.8 ± 1.4
$\frac{\text{Total cholesterol}}{\text{Lipid phosphorus}}$	50	14.5–31.6	22.9 ± 2.9	38	18.7–33.2	24.5 ± 3.1
Total protein (Gm. %)	34	6.12–8.21	7.32 ± 0.35	36	6.23–8.27	7.20 ± 0.38
Albumin (Gm. %)	34	3.27–5.02	3.94 ± 0.40	36	2.88–4.95	4.00 ± 0.32
Alpha globulin (Gm. %)	34	0.61–1.89	1.28 ± 0.19	36	0.37–1.90	1.29 ± 0.25
Beta globulin (Gm. %)	34	0.32–1.93	0.91 ± 0.23	36	0.35–1.54	0.89 ± 0.20
Gamma globulin (Gm. %)	34	0.11–2.24	1.07 ± 0.45	36	0.19–1.97	1.20 ± 0.40
Total globulin (Gm. %)	34	2.27–4.24	3.26 ± 0.34	36	2.16–4.31	3.33 ± 0.40
A/G Ratio	34	1.01–2.00	1.19 ± 0.22	36	0.67–2.29	1.19 ± 0.22

same free cholesterol value per 100 cc. in normal and atherosclerotic persons.

Table 1 shows that there was only a moderate increase in the phospholipid of the atherosclerotic, while the total cholesterol–lipid phosphorus ratio remained practically unchanged. Consequently, the only lipid fractions which are significantly altered in the atherosclerotic are the total lipids and total cholesterol.

Of the 39 total lipid and total cholesterol determinations performed, 24 revealed either an elevated total lipid, an elevated total cholesterol, or both. This abnormality involved about 60 per cent of the cases studied and cannot be considered statistically significant.

In order to determine whether the clinical condition of the patient might have an effect on the blood chemistry findings, most of the determinations were performed on seven patients while immobilized (during or immediately following a myocardial infarction) and during the recovery state which was at least four to six weeks after the acute attack (when few or no clinical symptoms were present). The results are listed in table 2.

The results show that there was very little difference between the phosphate fractions, the citric acid, and the protein fractions during the immobilized and the recovery states. Only in the lipid fractions did any significant differences appear. In three of the seven cases the total cholesterol was significantly higher in the recovery state than in the immobilized state (J. M., E. S., and C. C.). The total lipids, on the other hand, were higher in the recovery state than in the immobilized state in four cases (J. M., E. S., C. C., and T. K.). However, in two cases they were lower.

Consequently we note, as have many investigators before us, that there does exist a disturbance in lipid metabolism in the atherosclerotic, but, as manifested by plasma find-

TABLE 2.—*A Comparison of the Blood Chemistry Results Obtained for Atherosclerotics while Immobilized (i.e., During or Immediately Following an Attack) and while Ambulatory*

Patient	State	Inorganic Phosphorus mg. %	A.T.P. Phosphorus mg. %	Adenylic Acid P & Hexose Phosphate P, mg. %	Diphosphoglyceric Acid P mg. %	Total Organic Acid Soluble P mg. %	Citric Acid mg. %	Total Lipids mg. %	Total Cholest. mg. %	Free Cholest. mg. %	% Free Cholest.	Lipid Phosphorus mg. %	Tot. Chol./Lipid P	Total Protein Gm. %	Albumin Gm. %	Total Globulin Gm. %
E. T.	I	3.9	5.5	7.5	11.7	28.6	1.8	965	308	78.6	25.5	10.9	28.3	7.28	4.35	2.93
	R	4.3	4.2	6.5	9.8	24.8	1.6	957	314	88.7	28.3	12.7	24.7	7.29	3.74	3.55
J. S.	I	4.3	4.4	7.4	10.4	26.5	1.5	1070	314	10.4	33.1	12.7	24.7	7.06	3.54	3.52
	R	4.8	4.7	7.8	12.3	29.1	1.5	743	306	76.3	24.9	9.9	30.9	7.23	4.19	3.04
	I							887	281	79.6	28.3	13.0	21.6	6.88	3.39	3.49
J. M.	I	4.4	4.6	6.9	8.3	24.2	1.3	573	219	64.4	29.5	8.7	25.2	6.23	2.89	3.34
	R	4.8	5.7	7.6	11.5	29.6	1.4	900	313	86.7	27.7	11.9	26.3	7.48	3.60	3.88
H. S.	I	5.0	5.4	7.0	11.6	29.0	1.9	950	278	64.4	23.2	12.0	23.2	8.14	4.36	3.78
	R	4.7	4.2	6.5	9.4	24.4	1.5	767	306	76.0	24.8	11.1	26.4	7.10	3.83	3.27
E. S.	I	6.2	7.0	8.1	6.2	27.5	1.9	685	153	44.5	29.1	8.7	18.7	7.68	4.29	3.39
	R	5.8	4.8	6.7	7.9	25.2	1.5	1237	345	93.6	27.1	14.5	23.8	7.83	4.10	3.73
C. C.	R	3.9	4.7	7.4	10.9	26.9	2.1	1045	380	111	29.2	13.1	29.0			
	I	4.8	5.0	7.4	10.8	28.0	2.4	850	295					7.13	3.73	3.40
	R	5.6	4.9	8.0	9.6	28.1		860	342	84.7	24.7	11.8	29.0	7.64	3.83	3.81
T. K.	I							750	312	64.2	20.6	11.4	27.4			
	R	3.4	5.8	7.5	11.3	28.0	3.0	920	278	83.5	30.0	10.4	26.7			

I = immobilized state, R = recovery state.

ings, the disturbance is inconsistent and variable. The possibility remains that the ambulation of the patient and his nutritional state would influence the results obtained.

Complete autopsy examination of two of the studied cases (E. C. and T. K.) revealed extensive myocardial infarction due to coronary artery disease. The coronary arteries, aorta and the major arteries showed extensive atheromatous intimal disease. This consisted of extensive deposits of lipoid materials in the intima with narrowing of the lumen, calcification and fibrosis. The atheromatous deposits in the major vessels showed the usual distribution noted in cases of generalized arteriosclerosis.

TABLE 3.—*Blood Chemistry Results Obtained in Assorted Cases of Lipemia*

Determination	No. of Cases	Range mg. %	Mean mg. %
Inorganic Phosphorus	17	3.3–7.6	4.7 ± 0.8
Adenosine triphosphate Phosphorus	17	3.6–7.0	5.0 ± 0.7
Adenylic Acid Phosphorus and Hexose Phosphate Phosphorus	17	4.1–8.2	7.5 ± 0.7
Diphosphoglyceric Acid Phosphorus	17	6.7–14.0	10.9 ± 1.6
Total Organic Acid-Soluble Phosphorus	17	21.8–34.7	28.0 ± 2.6
Citric Acid	17	1.5–3.2	2.1 ± 0.3
Total Lipids	17	810–3513	1057 ± 470
Total Cholesterol	17	260–825	358 ± 109
Free Cholesterol	17	64.2–320	104 ± 57.4
% Free Cholesterol	17	21.9–77.9	29.1 ± 7.7
Lipid Phosphorus	17	9.6–30.6	15.8 ± 5.2
Total Cholesterol / Lipid Phosphorus	17	14.1–29.9	25.8 ± 3.9
	No. of Cases	**Range Gram %**	**Mean Gram %**
Total Protein	12	3.50–8.46	7.20 ± 1.12
Albumin	12	0.44–4.55	2.76 ± 1.13
Alpha Globulin	12	0.76–2.54	1.54 ± 0.31
Beta Globulin	12	0.22–1.58	1.00 ± 0.24
Gamma Globulin	12	0.13–2.91	0.92 ± 0.67
Total Globulin	12	2.45–5.96	3.68 ± 0.76
A/G Ratio	12	0.14–1.86	0.75 ± 0.44

In order to determine whether elevated plasma lipid in conditions other than atherosclerosis might influence the blood organic acid soluble phosphates, the serum citric acid or the serum proteins, these determinations along with the plasma lipids were performed on a series of assorted lipemics. Included were patients with hypothyroidism, biliary cirrhosis, cirrhosis of the liver, obstructive jaundice, diabetes, lipoid nephrosis, and other conditions all characterized by either a plasma total lipid of over 800 mg. per 100 cc. or a plasma total cholesterol of more than 300 mg. per 100 cc. The results are listed in table 3.

In this group of patients the phosphate fractions were not significantly different from the normal values. The mean for the citric acid was somewhat higher in these lipemic patients than the mean for the normal series. In the 12 patients in whom serum protein fractionations were performed, there was a distinct decrease in the mean albumin value with a smaller but significant increase in the mean total globulins. As far as the globulin fractions are concerned, only the alpha globulin differed significantly from the normal, the mean being slightly higher.

The above results show that in the lipemic patients as in the atherosclerotic patients the blood phosphate fractions and the serum citric acid are normal. The protein fractions, however, are abnormal. This may be related to a state of hepatic dysfunction or, as in the case of lipoid nephrosis included in this study, to a loss in albumin by glomerular filtration.

SUMMARY

1. Blood organic acid soluble fractions, including inorganic phosphorus, adenosine triphosphate phosphorus, adenylic and hexose phosphate phosphorus, diphosphoglyceric acid phosphorus, and total organic acid soluble phosphorus, serum citric acid, serum protein fractions, and plasma lipids including total lipids, total and free cholesterol, and lipid phosphorus were determined in a series of normal individuals and carefully diagnosed atherosclerotics.

2. No significant differences were revealed between the results obtained for the normals

and for the atherosclerotics except for the total lipids and the total cholesterol. Approximately 60 per cent of the 39 cases of atherosclerosis studied revealed either an elevated total lipid, total cholesterol, or both.

3. When a comparison of the blood chemistry findings was made in seven patients during the immobilized or acute state and the ambulatory or chronic state of myocardial infarction, again only the total lipids and the total cholesterol differed. However, the differences were inconsistent and variable.

4. The same series of determinations listed in paragraph 1 of this summary were performed on 17 patients with lipemias of various types. In this group only the serum protein fractions differed significantly from the values obtained in the normal subjects. The albumin was lower and the total globulin higher resulting in a diminished A/G ratio. Also, the mean for the alpha globulin fraction was significantly greater than the mean obtained for the normal series.

Sumario Español

1. Fracciones orgánicas ácido solubles sanguíneas incluyendo fósforo inorgánico, trifosfato de adenosina de fósforo, fósforo adenílico y hexosa fosfato de fósforo, ácido difosfoglicérico de fósforo y el total de fósforo orgánico ácido-soluble, ácido citrico del suero, fracciones proteínicas del suero y lípidos plasmáticos incluyendo lípidos totales, colesterol total y libre y fósforo lípido fueron determinados en una serie de individuos normales y en cuidadosamente diagnosticados ateroescleróticos.

2. Los resultados no revelaron diferencias significativas entre los normales y los ateroescleróticos excepto por los lípidos totales y el colesterol total. Aproximadamente 60 por ciento de los 39 casos de ateroesclerosis estudiados revelaron o un total de lípidos elevado, colesterol total, o ambos.

3. Cuando se hizo una comparación de los hallazgos de química de sangre en siete pacientes durante la inmobilización o el estado agudo y el estado ambulatorio o crónico de infarto del miocardio, otra vez los lípidos totales y el colesterol total solo difirieron. Sinembargo, las diferencias fueron inconsistentes y variables.

4. La misma serie de determinaciones enumeradas en el primer párrafo de este sumario fueron hechas en 17 pacientes con lipemias de varios tipos. En este grupo solamente las fracciones de las proteínas del suero difirieron significativamente de los valores obtenidos en los sujetos normales. La albumina fué más baja y la globulina más alta resultando en una proporción A/G disminuida. Además, el promedio de la fracción de globulina alfa fué significativamente mayor que el promedio obtenido en las series normales.

Acknowledgments

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Clinical Method of Photographing the Smaller Blood Vessels and the Circulating Blood in the Bulbar Conjunctiva of Human Subjects

By JØRN DITZEL, M.D., AND RICHARD W. ST. CLAIR, PH.C., FPSA

During a long-term study of the vascular disease of the smaller blood vessels in diabetes mellitus, the conjunctival vessels in more than 1200 diabetic and nondiabetic subjects have been examined. As part of the ideal delineation of these vessels it was found essential to develop a technic to produce highly magnified, wide-field photographs of the smaller blood vessels and of the circulating blood in human subjects. This technic is presented and the possibility of the clinical application is emphasized.

RECENTLY Knisely, Bloch and their associates[1, 2] have greatly improved the technics used in the field of microbiology of circulation. Their application of the stereoscopic, dissecting microscope to the study of the smaller blood vessels (arterioles, capillaries, venules) and the circulating blood in the bulbar conjunctiva of living individuals has also initiated a growing interest in capillary research in clinical medicine. The method is excellent for clinical use particularly since the vascular system of the bulbar conjunctiva (1) is easily accessible for study, (2) lies flat over a relatively large area and is not obscured by overlying tissue, (3) appears to be embryologically and anatomically related to the smaller blood vessels of the subcutaneous tissue and can reasonably be considered representative of this part of the vascular bed, and (4) permits a study of a statistically valid sample of the circulating *arterial* blood.[3] With this method, data concerning the status and the pathophysiologic reactions of the vessel walls and the circulating blood to various pathologic processes can be obtained.

The ideal delineation of the configurative and functional appearance of the conjunctival vessels and of the appearance of the circulating blood in them (aggregation of the red cells) may be gained by a combination of detailed microscopic observations and photographs of the field of interest. The direct observation gives optimal information about the over-all status of the components of the vascular bed, about transient changes as to the size and shape of the vessels and of the physical composition and the velocity of the circulating blood. The photographs give a permanent and accurate record of the changes, thus aiding the memory. They also permit comparisons so that differences in the capillary network and the circulation in it at various times can be established, thus minimizing the risk of bias.

In an attempt to evaluate the changes and the reactions in the conjunctival vascular bed in diabetic subjects[4, 5, 6] it was found helpful and essential to develop a method by which the smaller blood vessels and the circulating blood could be photographed under high magnifications. It is the purpose of this paper to describe such a method and give examples of some of the results gained from it.

PROBLEMS AND EARLIER EFFORT

The two main difficulties in taking photographs at relatively high magnifications of the human eye are to find: (1) A *set-up* by which an over-all sharp picture of a *convex* object in continuous movement (eye bulb and the circulating blood) can be produced. (2) A *light source* with sufficient intensity to take a short exposure and at the same time prevent damage

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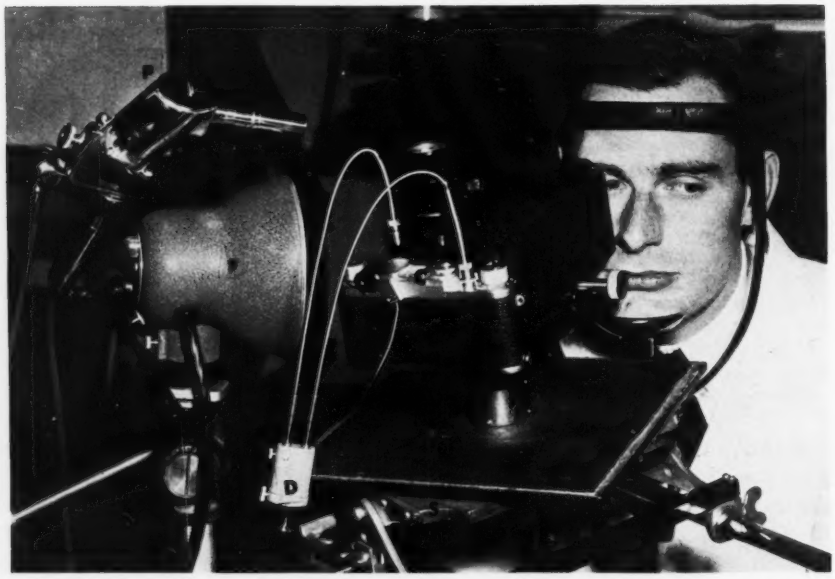

FIG. 1. Method of photographing the smaller blood vessels of the bulbar conjunctiva in human subjects.

C: Leica camera housing. *R:* Reflex housing (E. Leitz). *B:* Bellows attachment (E. Leitz). *P:* Shahan ophthalmic lamp (Mueller & Co., Chicago). *F:* Speed light (Heiland Strobonar IV). *D:* Double release. *H:* Ophthalmic head rest. *S:* Kelley-Koett x-Ray tube stand.

to the eye from either the light itself or from heat generated by the light.

The technic previously reported did achieve some success, but not complete acceptance.[7] Since it consisted of photographing through a monocular microscope tube, the results were rather diffuse, though a somewhat highly magnified picture was obtained. One of the disadvantages of such a system is due to the high light absorption and the fact that only a limited part, approximately 0.18 sq. cm., of the conjunctiva is in focus at any one time.

DESCRIPTION OF THE TECHNIC

In evaluating different methods it was found that the result could be improved considerably. The set-up best suitable for the purpose can be seen in figure 1. The patient has to be furnished with a comfortable chair together with some type of support which will hold the head immobile during the procedure and which is mounted on a firm table. Due to the fact that the patient and operator must face each other and be separated by only a short distance, an ophthalmic table which is supported on a single pillar and which may be raised and lowered quickly is very desirable. An ophthalmic head rest (*H*) which supports the chin and allows the forehead to rest against a ring support fulfills the requirements for immobilizing the head. A card illuminated with a low intensity light at some distance from the table is desirable as a target for the patient to look at. This will serve to quickly adjust the camera on the field in which the operator is interested and keep the eye immobilized for the exposure.

The photographic equipment must be of good design and construction and adjustable to the patient quickly. Because of the need for speed in operation only a few cameras are suitable. Since either black and white or color film may be desired, we have limited our work to the 35 mm. camera. For this use, either the Contax, the Exacta or the Leica are satisfactory. We have added the mirror reflex housing (*R*) and the bellow focussing device (*B*) to the Leica camera-housing (*C*). As objectives either the Leica enlarging lens of 50 mm. focal length or the Zeiss microtessar of 50 mm. are suitable. This basic equipment proved eminently satisfactory for our work.

The next problem is concerned with the camera support. An ideal support is the compound slide for the corneal microscope. When the camera is substituted for the corneal microscope it may be moved from side to side, forward and backward and up and down very quickly by means of the three knobs controlling these movements and at the same

time the instrument is very rigid. If this piece of equipment is not available, one can utilize equipment at his command which will do the same thing without too much trouble. However, it must be cautioned that if a substitution is made, this equipment must allow very rapid adjustment. For our purpose we have adapted an old Kelley Koett x-Ray tube stand (*S*).

From our experimental work we are convinced, that the electronic flash is the best light source available for this purpose. We have been using a Heiland Strobonar IV (*F*) with good results. This has a light output of 200 Watt-seconds or a guide number of 70 under ordinary conditions for Kodachrome. This will allow a diaphragm opening of about 16 to 32 under normal working conditions, which gives the needed depth of field to cover the curvature of the eye. The only disadvantage we have encountered is the lack of a pilot light in the reflector.* Since the wet surface of the eye is liable to give undesirable reflections in the field, this could be omitted if we could visualize where our light was striking. Up to the present time we have used a Shahan ophthalmic lamp (*P*) as close to the flash unit as possible for focussing and in an attempt to obviate this fault as much as possible. This lighting equipment has been set up about 25 to 35 cm. from the eye and shielded with an additional piece of lucite plate, 0.5 cm. in thickness to act as a safeguard in case of explosion of the flash tube. The smaller blood vessels in the most lateral part of the bulbar conjunctiva are selected for this work. By using the reflex housing it was possible to select a suitable field and bring the vessels into sharp focus and keep them in focus up to the instant the exposure was made. Even patients with relatively severe photophobia have been photographed without discomfort due to the very short exposure of the electronic flash lamp 0.001 to 0.0001 second.

In photographing patients we usually assembled the various components in advance. When the patient arrives it is necessary only to have him take his seat, adjust the height of the head rest and focus. The exposure is made by means of the double cable release (*D*), to which the mirror, shutter and electronic flash are all integrated. Generally several exposures are made in rapid succession, and the entire procedure will not take over five minutes.

Several other methods have been tried. In one we placed the patient in a recumbent position and arranged the equipment vertically. While this eliminates the head rest and table, there is a chance of rotation of the head and it is much more difficult for the operator to work above the patient. We have also used a Grenough type dissecting microscope with the camera set up in one telescope and the focusing done through the other. This method has the following disadvantages: diaphragming is not possible, exposures have to be quite long when a constant light source is used, due to the absorption of light by the prisms, and are inadequate with an electronic flash of 200 watt-seconds. Finally we have experimented with larger plate cameras with long bellows extension. The disadvantage of such a method is that the time between focusing, inserting the plate and making the exposure is so long that the patient may move and thus change the field or the focus or both.

* We have been told by the Dormitzer Company, Hadley Street, Cambridge, Mass., that they have built lighting units on special order which incorporate a pilot light along with the flash tube.

Result and Discussion

The negative obtained with this equipment has a magnification of approximately 5.5 times and has a sufficiently wide field. It shows a distinct image of the configuration of the vessels and circulating blood. The procedure yields such good results that the ultimate positive can be enlarged to 8 by 10 inches or even 11 by 14 inches without loss of definition.

An example is shown in figure 2. The course of the peripheral vascular components can easily be traced. The arterioles (*a*) run parallel to the larger venules and bifurcate at regular intervals to finally form the capillaries (*c*), which again join into the venules (*v*). From the picture the composition of the circulating blood can also be observed. It is clearly demonstrated that the blood cells in the vessels of this patient are aggregated to form intravascular clumps of various sizes. This clumping is most extensive in the capillaries (*s.c*) and in the venules (*s.v*), where the rate of flow normally is most decreased. Along the course of the arterioles it is often difficult to record visually the presence of clumping on account of the rapidity of blood flow in this part of the network. The photograph, however, clearly reveals that the blood column in the arterioles is separated by "plasma" spaces as an indication of the existence of aggregation (*s.a*). The aggregates, which are caused by changes in the relative amounts of colloids in the plasma, are often able periodically to plug the lumen of the smaller blood vessels and decrease the rate of the blood flow considerably, particularly in the capillaries and in the smaller venules. Evidences that this aggregation is an essential fac-

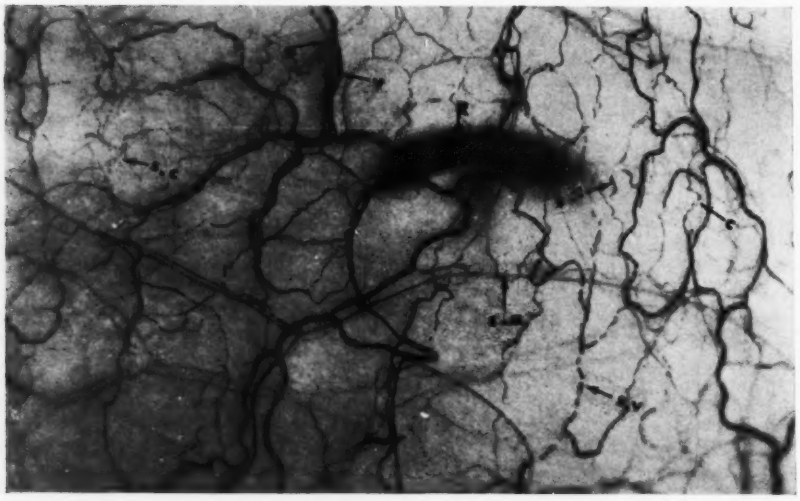

FIG. 2. The vascular bed of the bulbar conjunctiva in a young woman with diabetes mellitus. Note the course of the arterioles (*a*), the capillaries (*c*) and the venules (*v*). Note the marked intravascular aggregation of the blood cells in the arterioles (*s.a.*), in the capillaries (*s.c.*) and in the venules (*s.v.*). See text. (Magnification 54×.)

tor in the development of degenerative changes in the smaller blood vessels have been given by Knisely and his coworkers[3] and by Ditzel and associates.[4, 5, 6]

It is not the purpose in this paper to describe the changes of the conjunctival vascular bed in diabetes, which previously have been reported in detail[4, 6]; we only wish to emphasize the clinical possibilities of the method by giving the data obtained from a single conjunctival examination based on the combined direct microscopic observation and the picture presented (fig. 2).

Case 827. A 24 year old female, with diabetes mellitus of six years duration, was receiving 64 units of insulin daily. Examination of the urine revealed no albumin or ketone bodies. The nonprotein nitrogen was 31 mg. per 100 cc. The hemoglobin was 85 per cent, the red blood cell count 4.5 million, the erythrocyte sedimentation rate 29 mm. in 1 hour. The capillary fragility test produced less than 20 petechiae. No retinopathy was present. Atherosclerosis was not seen in x-ray films of the tibial and pelvic arteries and the aorta. The blood pressure was 120/75.

Microscopic observation of the lateral parts of the bulbar conjunctiva by Knisely's method.[1] *Arteriolar* configuration (*a*) shows generally a regular and even course, but in a few places constant irregularities can be observed suggesting the beginning of arteriolosclerosis. The diameter of the arterioles, just before their division into terminal arterioles, measure approximately 15 microns. The circulating blood in the arterioles contains aggregates of blood cells. These can be observed at the tip of the arterioles, since the aggregates stop there momentarily before they are squeezed slowly through the capillaries. (See fig. 2, *s.a.*)

The *capillary network* is irregular. The venous part of approximately 75 per cent of the capillaries is elongated showing fixed angularities and smaller irregularities in the configuration (focal nodularities and a few constrictions) (*c*). The normal unbroken column of circulating blood cells in the capillaries is not seen. Instead aggregates of various sizes from 18 to approximately 120 microns in length and 9 microns in width are found (*s.c.*). The rate of blood flow is considerably reduced.

The configuration of the *venules* show in many places irregularities and in a few places sausage-shaped sacculations. The larger venules (more than 36 microns) are slightly distended and the ratio between the diameter of the arterioles and the venules is from 1:5 to 1:3 (normal from 1:3 to 1:2).[4] The course of the venules is elongated and irregular. The rate of flow in the venules up to 60 microns in diameter is reduced, since the course of the individual aggregates easily can be followed. (*s.v.*).[3] In the larger venules the rate of flow is again so rapid that no aggregates can be seen. The aggregates measure in length more than 100 microns and fill up the lumen of the venules and in this way

obscure the peripheral layer of plasma. No clumps of white cells are seen.

From the smaller venules measuring between approximately 12 and 27 microns in diameter, leakage of plasma is indicated since hemoconcentration in the vessels and edema in the perivascular tissue is visible.

Summary

A clinical method of photographing the smaller blood vessels of the bulbar conjunctiva in man and the blood circulating in them is presented.

The possibilities of studying the pathophysiologic reactions and the status of the smaller blood vessels by means of this technic have been outlined and are illustrated by the interpretation of the vascular and hemodynamic changes deduced from the combination of direct microscopic observation and the photograph of the vascular bed of the bulbar conjunctiva of a young woman with diabetes mellitus of six years' duration.

Sumario Español

Un método clínico para fotografiar los vasos sanguíneos pequeños de la conjuntiva bulbar en el hombre y la sangre que circula por ellos se presenta.

Las posibilidades de estudiar las reacciones patofisiológicas y el estado de los vasos más pequeños por medio de esta técnica han sido bosquejados y se ilustran por medio de la interpretación de los cambios vasculares y hemodinámicos deducidos de una fotografía de la cama vascular de la conjuntiva bulbar de una mujer joven con diabetis mellitus de seis años de duración.

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CLINICAL PROGRESS

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Syndrome of Short P-R Interval with Abnormal QRS Complexes and Paroxysmal Tachycardia (Wolff-Parkinson-White Syndrome)

By LOUIS WOLFF, M.D.

THE syndrome of short P-R interval with abnormal QRS complexes and paroxysmal tachycardia was first described in 1930.[1] Attention was called to its occurrence in young healthy individuals with normal hearts, to the frequency of paroxysmal tachycardia, to the unusually short P-R interval with abnormal QRS complexes, and to the spontaneous or induced change from the abnormal to a normal electrocardiogram, or the reverse. These are now universally recognized as the distinguishing features of this syndrome, which was thus established on a firm clinical and electrocardiographic basis for the first time.[1] However, the nature of the disorder was left in doubt.

TERMINOLOGY AND DESCRIPTION

About 300 articles dealing with this anomaly have been published, and many of the authors have ventured to name the syndrome. The names most commonly used are the Wolff-Parkinson-White syndrome (W-P-W syndrome), anomalous atrioventricular excitation, the syndrome of short P-R interval with abnormal QRS complexes and paroxysmal tachycardia, pre-excitation, and the bundle of Kent syndrome.

The features which distinguish the syndrome are the peculiar electrocardiogram and paroxysmal rapid heart action. The P-R interval is 0.10 second or less in about 85 per cent of the cases, and is rarely greater than 0.12 second. The QRS complex measures 0.11 to 0.12 second in almost half of the cases, but may be as long as 0.20 second, or within normal limits in occasional instances. A characteristic feature of the ventricular complex is heavy slurring of the initial deflection of the QRS group. Gross notching of the QRS complex sometimes occurs; and QS deflections are not infrequently seen in leads II, III, aV_F, the superior esophageal, and the right-sided precordial leads. Q waves do not occur in the left-sided precordial leads (fig. 1). An observation noted in the first case studied by us,[1] and one which is a noteworthy feature of the syndrome, is the spontaneous or induced transformation of the electrocardiogram: the P-R interval lengthens but remains within normal limits, and the QRS complex assumes normal proportions and morphology (fig. 2).

The abnormal mechanism is called the anomalous mechanism, or anomalous atrioventricular excitation. When it prevails the short P-R interval is referred to as the anomalous or abnormal P-R interval; the QRS complex is variously designated as the anomalous, abnormal, or aberrant QRS or ventricular complex; and the heavily slurred deflection which initiates the QRS group is called the anomalous or premature component of QRS. The last has also been called the delta wave. When the normal type of tracing occurs the designations used are the normal P-R interval and normal QRS or ventricular complex, even if abnormalities, other than those inherent in anomalous excitation, are evident.

The paroxysmal rapid heart action is always

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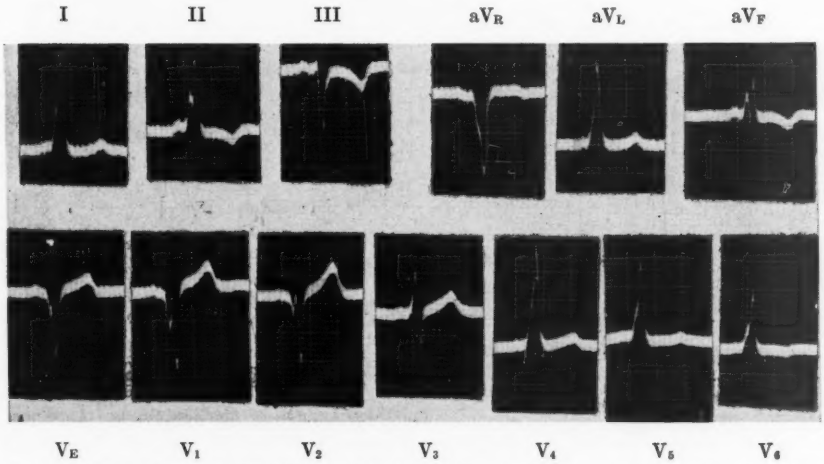

FIG. 1. Short P-R interval and abnormal QRS complexes in a 20 year old man with a normal heart. The tracing resembles left bundle-branch block in many ways. However, the P-R interval is 0.08 to 0.10 second, and since the P waves are upright in the standard limb leads and inverted in aV_R, a normal sinoauricular mechanism is present. The P-J interval is 0.26 second. The premature, or anomalous, component (delta wave) of the QRS complex is best seen in V_5 and V_6 as the heavily slurred initial part of the ascending limb of the R wave; notching of QRS is seen in leads II, aV_F, V_1, and V_2. Note the QS deflections in leads V_E, V_1, and V_2, and the absence of Q waves in the left sided precordial leads. The T waves are inverted in leads II, III, aV_F, and V_6. Precordial leads recorded at half normal standardization.

(Same as figure 102, p. 175, *Electrocardiography: Fundamentals and Clinical Application*, by Louis Wolff, M.D., Philadelphia, W. B. Saunders Co. Reproduced by courtesy of the Publishers.)

of the supraventricular variety. The most common type resembles paroxysmal auricular tachycardia, but paroxysmal auricular fibrillation and paroxysmal auricular flutter also occur.

ETIOLOGY

The disorder is, in all probability, of congenital origin. The increasing number of cases observed in infants supports this concept. Since the abnormal mechanism may be latent for years, its demonstration, for the first time late in life cannot be considered evidence of its initial appearance. There is no proof that the syndrome is acquired. Recently, however, aberrant ventricular complexes have been noted during and immediately following cardiac catheterization,[2, 3] as well as in animal experiments in which subthreshold stimuli were used to enhance the irritability of the ventricular musculature,[4] and their resemblance to the anomalous complexes in cases of the Wolff-Parkinson-White syndrome has been commented upon. It is impossible to differentiate these from ventricular premature beats arising immediately after the onset of auricular systole.

MECHANISM

It is generally agreed that premature activation of a small fraction of ventricular musculature is responsible for both the short P-R interval and the abnormally wide QRS complex. There is still considerable difference of opinion, however, concerning the manner in which pre-excitation is brought about. These opinions embrace two concepts: the one supposing the mechanism to be an anomaly of impulse formation, the other that it is an anomaly of conduction. The former invokes the existence of an irritable center below the A-V node which discharges an impulse immediately after the onset of auricular systole. The latter presupposes that action currents set up in the auricles during auricular systole are conducted, with or without the aid of a structural path-

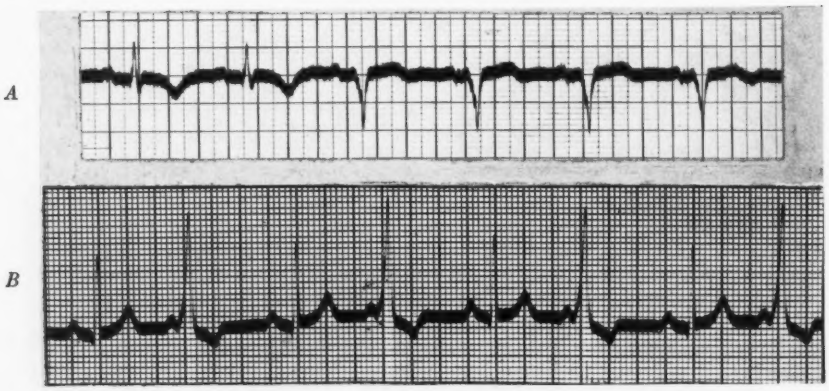

FIG. 2. Spontaneous shift between normal and abnormal beats. *A*, The first two beats are normal, the remaining ones anomalous. *B*, Another case with alternate normal and abnormal complexes, actually 2:1 block of the accessory pathway. In the normal beats the P-R and QRS intervals are 0.18 and 0.08 second, respectively, there is a small Q wave followed by an R deflection with a sharp upstroke, and an upright T wave. The corresponding intervals in the abnormal beats are 0.08 and 0.13 second, respectively, the Q wave has disappeared, the R wave is much taller and is initiated by a heavily slurred component (premature or anomalous component, delta wave), and the T wave is inverted. The premature component of the anomalous QRS complex encroaches on the P wave, but the portion of the latter which remains visible is identical to the corresponding part of the auricular deflection of the normal beats. The difference between the normal and abnormal P-R intervals is 0.10 second; anomalous depolarization is so premature that the excitation wave approaching the ventricles along the normal A-V connections everywhere encounters refractory muscle; therefore, the entire ventricular myocardium is depolarized via the anomalous route; the normal P-J interval is 0.26 second, and the anomalous P-J interval is 0.21 second.

(Same as figure 108, p. 179, *Electrocardiography: Fundamentals and Clinical Application*, by Louis Wolff, M.D. Philadelphia, W. B. Saunders Co. Reproduced by courtesy of the Publishers.)

way, to the ventricular musculature in accelerated fashion; Kent and others have described accessory A-V connections, and these have been demonstrated at autopsy in some of the patients with the Wolff-Parkinson-White syndrome. In either case, the A-V node, the natural stumbling block to conduction, is circumnavigated, and auriculoventricular conduction time is consequently abbreviated.

The hypothetic pathway of accelerated conduction, or the anomalous center of impulse formation, cannot involve the A-V connecting tissues in their entirety, for there is evidence that these tissues conduct action currents from the auricles to the ventricles in an entirely normal manner at varying intervals after the onset of the premature ventricular depolarization. That is, the ventricles are subjected to a dual innervation, and are invaded by two separate and independent waves of depolarization. The anomalous one starts first, and is followed by the normal wave a fraction of a second later, the precise time depending on the length of the normal P-R interval. The interval separating the onset of ventricular depolarization via these two separate pathways subtracted from the normal P-R interval corresponds to the anomalous P-R interval, and when added to the normal QRS interval corresponds to the anomalous QRS interval. It is for this reason that the P-J intervals (P-R plus QRS intervals) are identical, or nearly so, in both anomalous and normal beats when both are present in the same electrocardiogram.[5, 6] The exceptions are those cases in which anomalous depolarization begins so prematurely and, therefore, involves so much of the ventricular musculature via the anomalous pathway, that the oncoming normal excitation wave everywhere encounters active (refractory) myocardium. Under these circumstances ventricular depolarization takes place in an

entirely anomalous manner. In these cases the anomalous P-J interval is shorter than the normal one.

Whether ventricular depolarization occurs in the one way or the other, its onset invariably is via the anomalous route, and appears to proceed from epicardium to endocardium. This reversal in direction of ventricular activation alters the initial and early resultant cardiac vectors sufficiently to preclude the development of those QRS signs upon which a diagnosis of myocardial infarction is based.[7, 8]

The anomalous mechanism may remain latent for indefinite periods of time, yet it may be possible to induce the appearance of the abnormal electrocardiogram, or the latter ultimately may emerge spontaneously. The abnormal mechanism may appear and disappear in an unpredictable manner, and rare instances in which normal and anomalous beats alternate have been observed (fig. 2*B*). The abnormal mechanism can be suppressed with certain drugs or procedures.

Paroxysmal rapid heart action occurs in at least 70 per cent of all recognized cases of the Wolff-Parkinson-White syndrome (the incidence is much higher in infants and young children) and must be considered an integral part of the disorder. In all probability the mechanism which is responsible for the abnormal electrocardiogram is also responsible for the paroxysmal tachycardia. It is not difficult to imagine the inception of circus movement following re-entry of the normal excitation wave by retrograde conduction through an accessory conducting pathway. Actually, paroxysmal tachycardia has been produced experimentally in this manner. On the other hand, an irritable anomalous center of impulse formation is an equally adequate explanation for the ectopic rhythm. Nevertheless, although the abnormal electrocardiogram and the paroxysmal tachycardia may arise from a single mechanism, both need not necessarily be in evidence at the same time. In fact, the ventricular complex during paroxysms of tachycardia is usually normal, and only occasionally is the anomalous form observed with the rapid heart rates.

The Clinical Picture

The syndrome is seen in all age groups. It is most frequently recognized in those age groups in which electrocardiograms are most commonly obtained. Because of the growing custom of obtaining electrocardiograms more or less routinely, it is being observed with increasing frequency in infants and young children. Many cases are being discovered in the military services, in the course of insurance and industrial examinations, and in mass health surveys. Seventy per cent of the patients are males.

The most common clinical feature is paroxysmal rapid heart action which occurs in well over 70 per cent of the individuals whose electrocardiograms at some time or other display anomalous atrioventricular excitation. The paroxysms may begin at birth, during infancy, in childhood, or in adult life. Paroxysmal tachycardia may occur for the first time at an advanced age, many years after the peculiar electrocardiogram is first observed. Symptoms associated with paroxysmal tachycardia are usually not severe, but result in invalidism in occasional patients. Sudden death rarely occurs. Some patients become chronic invalids despite normal hearts, as the result of a diagnosis of serious heart disease based on misinterpretation of the anomalous electrocardiogram. In general, however, the health of patients with the Wolff-Parkinson-White syndrome is good, and restriction of activity is not necessary. Strenuous exertion need not be proscribed. Indeed, many of our patients were healthy, vigorous athletes, accustomed to strenuous activity, and some were exposed to and tolerated well the hardships and rigors of military life.

Examination of the heart is not remarkable in most of the individuals whose electrocardiograms display anomalous atrioventricular excitation. The first apical sound is often reduplicated, and benign murmurs occur. The blood pressure is normal. The cardiac rhythm is regular, but when the anomalous mechanism prevails the heart rate is usually slow and sinus arrhythmia is common. Auricular or ventricular premature beats occur now and then, and during paroxysms the features of

paroxysmal auricular tachycardia, auricular fibrillation, or auricular flutter are noted. Visceral congestion, or other evidences of heart failure, never occurs, except in the rare instance of uncontrolled tachycardia persisting for an indefinite length of time.

The signs of congenital heart disease, or other congenital anomalies, are rarely noted; and the signs of acquired heart disease or hypertension may be observed. These findings are coincidental and bear no fundamental relation to the syndrome. The incidence of diseases other than those involving the cardiovascular system appears to be the same as in the general population. Intercurrent disease, pregnancy and childbirth, and surgical procedures are not influenced by the syndrome, nor does the latter increase the incidence of cardiac complications, except for the proneness to paroxysmal tachycardia. The syndrome is not a contraindication to pregnancy or operation.

Electrocardiographic Features

The characteristic electrocardiographic features of anomalous auriculoventricular excitation are the unusually short P-R interval and the abnormally wide QRS complex. The short P-R interval is diagnostic only in the presence of normal P waves indicative of sinoauricular rhythm. The P-R interval is 0.10 second or less, and the QRS interval is 0.10 to 0.20 second in most cases. QS deflections may occur in leads II, III, aV_F, the superior esophageal, and the right-sided precordial leads; QR deflections do not occur in the left-sided precordial leads. A characteristic morphologic feature is the heavily slurred anomalous component which initiates the QRS group of deflections, and there may be notching of QRS. The instantaneous electrical axis of the anomalous QRS is normal in one-third of the cases, deviated to the left in one-half, and to the right in one-sixth of the cases. The S-T segments are isoelectric or slightly or markedly displaced from the base line, and the T waves vary from normal to deeply inverted. Instability of the S-T segments and T waves is a striking feature (fig. 1).

A noteworthy aspect of the electrocardiogram, and one which is of considerable diagnostic importance, is the shifting, back and forth, from anomalous to normal auriculoventricular excitation. This occurs spontaneously, or can be induced with certain drugs and procedures. The change occurs spontaneously in more than one-half of the cases in an unpredictable manner; normal and abnormal complexes may alternate regularly, or varying combinations of them may occur. Repeated observation over a period of years may disclose only the abnormal type of tracing, or just one of many electrocardiograms at the beginning or end of a long series of graphs may reveal anomalous conduction. Anomalous conduction will be induced in some cases by carotid sinus stimulation, the vagotonic action of atropine, or the administration of digitalis. This effect of digitalis persists several hours at the most, and may become evident only upon carotid sinus stimulation or forced expiration. The abnormal mechanism can be suppressed by exercise, the vagolytic action of atropine, quinidine, amyl nitrite inhalation, procaine amide, deep inspiration, or various combinations of these. Anomalous conduction is precluded when the pacemaker is displaced to the lower reaches of the A-V node, and by some auricular premature beats.

When the anomalous mechanism is suppressed the P-R interval lengthens and the QRS interval shortens, both attaining normal values. Concomitantly the morphology of the QRS and T deflections reverts to normal, the S-T segments return to the isoelectric level, and normal QR deflections appear, providing the heart is normal, and drugs which alter the electrocardiogram have not been exhibited. The instantaneous electrical axis also changes and is normal in 80 per cent of the cases, and deviated to the left in the rest. If there is complicating heart disease and other electrocardiographic abnormalities, these become evident when the anomalous mechanism is suppressed. Then the characteristic QRS, S-T segment, and T-wave abnormalities of myocardial infarction (fig. 3) or the diagnostic features of left ventricular hypertrophy emerge, or right bundle branch block appears.

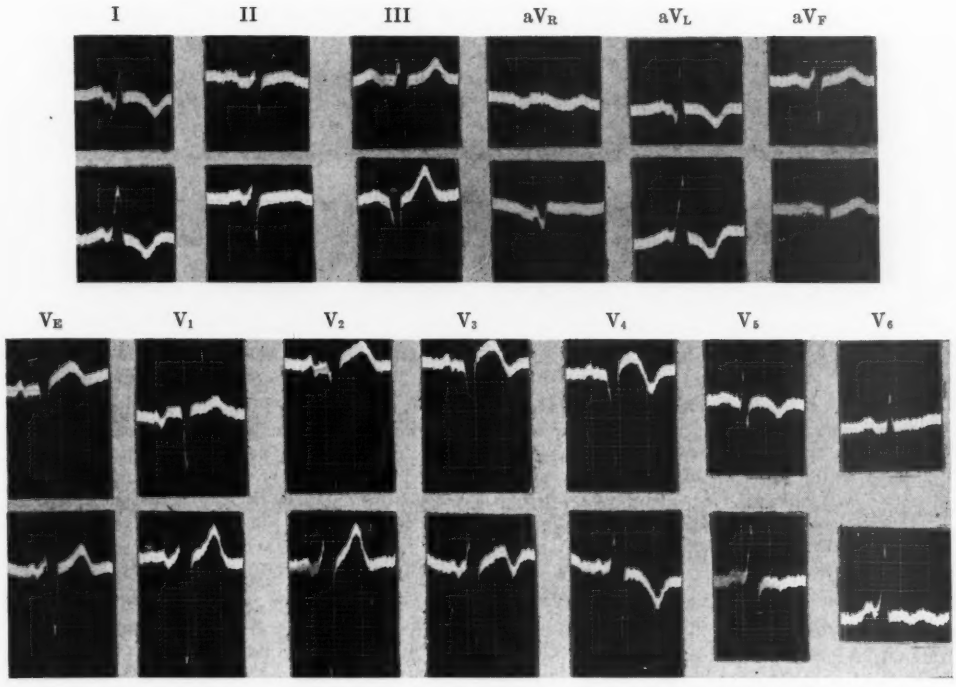

FIG. 3. Limb and precordial leads during normal A-V conduction and anomalous A-V conduction in a 50 year old man with an acute anterior myocardial infarct. Top and third rows: Limb and precordial leads during normal A-V conduction. Second and bottom rows: Limb and precordial leads during anomalous A-V conduction. Signs of anterior infarction present with normal conduction, absent with anomalous conduction.

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PAROXYSMAL RAPID HEART ACTION

Electrocardiograms recorded during paroxysms of rapid heart action reveal the presence of normal ventricular complexes in most instances. The diagnosis of supraventricular tachycardia, auricular fibrillation, or auricular flutter offers no difficulty in these.

A small number of electrocardiograms obtained during paroxysms disclose abnormal ventricular complexes, and most of these have been called paroxysmal ventricular tachycardia by the authors reporting them. However, we have pointed out elsewhere that the abnormal ventricular complexes of the paroxysm are similar to the anomalous beats occurring between paroxysms when a normal sinoauricular rhythm exists, that in some tracings auricular deflections are regularly paired with the ventricular complexes, while in others the basic rhythm is auricular flutter with an established or shifting grade of partial auriculoventricular block. We have also observed the occurrence of more than one type of abnormal ventricular complex in different paroxysms, and have noted the same variety of anomalous complexes between paroxysms when the cardiac pacemaker was in the sinoauricular node. For these reasons we believe that most, if not all, of the cases diagnosed as paroxysmal ventricular tachycardia are in reality supraventricular paroxysms distinguished by the persistence of anomalous auriculoventricular excitation. We have not

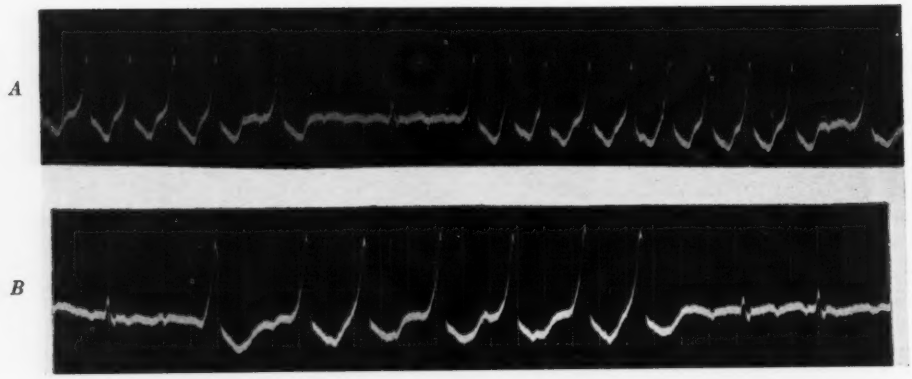

FIG. 4. *A*, Runs of anomalous ventricular complexes at an extremely fast rate, replacing normal ventricular complexes occurring at a slower rate. One normal ventricular complex is seen in the middle of the strip. The anomalous complexes are identical to those which occurred prior to and following the paroxysm during the existence of normal sinus rhythm and unusually short P-R intervals. *B*, during the same paroxysm, after spontaneous slowing of the anomalous responses. The anomalous and the normal beats occur at about the same rate, and both are absolutely irregular; at this time there can be no confusion with paroxysmal ventricular tachycardia.

seen undoubted examples of paroxysmal ventricular tachycardia in uncomplicated cases of the Wolff-Parkinson-White syndrome.

A typical and not uncommon example of persistence of anomalous excitation during rapid heart action is seen in paroxysmal auricular fibrillation. This is characterized by runs of anomalous ventricular complexes at extremely fast rates replacing or interrupting normal ventricular complexes occurring at a slower rate (fig. 4). Most published examples of this sort have been incorrectly interpreted as paroxysmal ventricular tachycardia. The correct diagnosis can be made if the patient is known to have the Wolff-Parkinson-White syndrome, or should be suspected if the heavily slurred premature component initiating the QRS complex is noted. The diagnosis is certain if the rapid ventricular complexes are morphologically similar to the anomalous beats recorded at other times during sinoauricular rhythm.

As a rule digitalis is ineffective in slowing the rapid anomalous ventricular responses. Indeed, this drug often appears to increase the number and rate of anomalous beats, and to perpetuate the arrhythmia. Quinidine effectively blocks the anomalous pathway, slowing the rate at which anomalous beats are conducted to the ventricles, or interrupting these responses completely.

DIAGNOSIS

A mistaken diagnosis of heart disease had been made in more than one-third of our cases.[6] The basis for error was an erroneous appraisal of benign murmurs, interpretation of the split first apical sound as a gallop rhythm or a mitral diastolic murmur, and failure to appreciate the part played by paroxysmal rapid heart action in producing symptoms. By far the most important cause of error, however, was misinterpretation of the electrocardiogram.

Diagnosis of the Wolff-Parkinson-White syndrome cannot be made in the absence of the characteristic electrocardiographic features which distinguish this disorder, namely, the unusually short P-R interval and the abnormal QRS complex. The short P-R interval is diagnostic only when the P waves are normal, and, therefore, indicative of a sinoauricular cardiac mechanism. The diagnosis can be made on the basis of a P-R interval of 0.10 second or less, if normal P waves are present, even if the QRS complex is normal. There is no other condition in which P-R intervals of such brevity exist when the heart

is under sinoauricular control. The same is probably true for P-R intervals up to 0.12 second, but as this level is approached, and certainly when it is exceeded, additional data must be available if the diagnosis is to be made, especially if the QRS complex is normal. In such cases the spontaneous or induced transformation from a normal to an abnormal mechanism, or the reverse, with the consequent characteristic changes in the P-R and QRS intervals, furnishes the necessary diagnostic evidence. Electrocardiograms in which measurements of the various intervals or the morphologic features of the ventricular complex are equivocal are not uncommon.

The diagnosis of the Wolff-Parkinson-White syndrome should be considered under the following circumstances: (1) when the P-R interval is 0.12 second or less and the QRS complex is abnormal, (2) when runs of abnormal ventricular complexes at a fast rate occur during paroxysms of auricular fibrillation, (3) when the tracing suggests bundle branch block, (4) when tracings change spontaneously, particularly if the P-R and QRS intervals change in opposite directions, (5) when the initial component of the QRS group is heavily slurred, and (6) in every patient with paroxysmal tachycardia. It should be remembered that patients seen for the first time during paroxysmal tachycardia may have received quinidine, which may have temporarily suppressed the anomalous mechanism.

The recognition of anomalous auriculoventricular excitation is of considerable importance for three reasons. The first of these is that the tracing, by virtue of its obviously abnormal appearance, frequently leads to an erroneous diagnosis of heart disease. The most common errors of interpretation are myocardial infarction, myocarditis, left or right ventricular hypertrophy, and bundle-branch block. The incorrect diagnosis of myocardial infarction can be avoided if it is remembered that QS deflections commonly occur in leads II, III, aV_F, and the right sided precordial leads, and that the S-T segments and T waves are naturally unstable in the syndrome under discussion, and, therefore, subject to spontaneous, unexplained variations.[8] The P-J interval (sum of P-R and QRS intervals) is 0.26 second or less in most cases of the Wolff-Parkinson-White syndrome, and is greater than 0.26 second in most cases of bundle branch block. Furthermore, right bundle-branch block and anomalous auriculoventricular excitation can be differentiated by noting in the latter late "intrinsicoid" deflections in both the right and left sided precordial leads. Most errors in diagnosis will be avoided if the sound principle of refraining from making an additional electrocardiographic interpretation in tracings displaying anomalous excitation is adhered to. Finally, routine measurement of the P-R interval is the best safeguard against overlooking the syndrome. This should be done in all three standard limb leads, since the anomalous component may be isoelectric in one of them; if the measurements are made in the latter the P-R interval will appear longer, and the QRS interval shorter than they actually are.

The second reason why it is important to recognize anomalous excitation is that it masks various abnormalities. The most serious of these is myocardial infarction. Therefore, this diagnosis should never be excluded in patients with anomalous excitation merely because the electrocardiogram does not display the diagnostic QRS signs of this lesion. Suppression of the anomalous mechanism will unmask the signs of infarction, providing such a lesion exists.[8] The electrocardiographic signs of left and right ventricular hypertrophy and right bundle branch block are also masked by anomalous excitation, and will become evident when the anomalous mechanism is suppressed.

Finally, the recognition of anomalous conduction is important because of the extremely high incidence of associated paroxysmal rapid heart action. This may point the way to the diagnosis of paroxysmal tachycardia in infants, in whom it is often an elusive diagnosis, and not rarely a fatal condition if untreated. Furthermore, in any patient, the diagnosis of anomalous excitation may call attention to the possibility that paroxysmal tachycardia is the explanation of an obscure clinical picture. Lastly, the knowledge

that a given individual has anomalous excitation may bar him from occupations in which the sudden onset of tachycardia might be hazardous.

Prognosis

There are no subjective manifestations associated with anomalous auriculoventricular excitation per se. The disorder is entirely asymptomatic and of no more than academic interest in those who have never had paroxysmal rapid heart action. Symptoms occur exclusively during the progress of paroxysmal tachycardia, or during its onset or offset. Clinical manifestations, when they do occur, are not severe, as a rule, since the heart is normal otherwise in the majority of cases.[9] Most patients are able to live a normal, active, and even strenuous life. Occasionally, however, disability is severe, or activity is limited because of the unpredictability of paroxysmal tachycardia with consequent faintness, diminished mental alertness, loss of consciousness, or other ill effects. The occurrence of sudden death has been reported by several authors. Life Insurance experience indicates that applicants with the Wolff-Parkinson-White syndrome are not standard risks in that their mortality rate is approximately three times the normal.[10]

Management of Patients with the Wolff-Parkinson-White Syndrome

The anomalous electrocardiogram itself is of no clinical significance and attempts to alter it should be made only for diagnostic purposes in questionable cases, or for unmasking other abnormalities. The various types of paroxysmal rapid heart action respond to the standard therapeutic measures in the same manner as in patients who do not have anomalous excitation, with one exception, namely, runs of anomalous beats at extremely rapid rates occurring during the course of paroxysmal auricular fibrillation (fig. 4). Control of the ventricular rate in these cases cannot be achieved with digitalis, and the tendency to give increasing amounts of the drug frequently leads to digitalis intoxication. The most effective treatment is quinidine, which blocks the anomalous mechanism and may, at the same time, abolish the auricular fibrillation.

Prevention of paroxysms is achieved with the same drugs and regimen as in cases of paroxysmal tachycardia not having the Wolff-Parkinson-White syndrome.

Special care during pregnancy or child birth, and special preparation preoperatively are not necessary, except in patients who at other times have frequent attacks of paroxysmal tachycardia. The standard and proved prophylactic measures should be employed in these individuals.

Activity should in no way be curtailed except when it predisposes to paroxysms, but patients should be discouraged from engaging in occupations in which sudden tachycardia might prove dangerous.

Summary

The syndrome of short P-R interval with abnormal QRS complexes and paroxysmal tachycardia occurs in otherwise healthy individuals in all age groups. Its interest and importance are related to our knowledge and concepts of the cardiac mechanism, the prevalence and clinical manifestations of paroxysmal tachycardia, the masking of the electrocardiographic signs of heart disease, and the serious consequences involved in making an incorrect diagnosis of heart disease.

A single mechanism is in all probability responsible for the abnormal electrocardiogram and the paroxysmal tachycardia. Premature activation of a small fraction of ventricular musculature shortens the P-R interval and lengthens the QRS interval, thus accounting for the electrocardiographic peculiarities of the syndrome. Whether an anomaly of impulse formation or an anomaly of conduction is responsible for pre-excitation is not known, and the propensity to paroxysmal tachycardia can be explained on either basis. There is no evidence that hitherto unknown phenomena are responsible for the syndrome. The disorder is probably congenital in nature.

A noteworthy feature is the spontaneous or induced shift, back and forth, from the abnormal to the normal type of electrocardic-

g am. Many drugs and procedures are a ailable for this purpose. This is of immeasu able help in establishing the diagnosis of the W olff-Parkinson-White syndrome in doubtful ca ses, and in unmasking the many abnormalities which anomalous excitation conceals.

Diagnostic errors are common, and the re asons for these have been discussed. Myocardial infarction, mitral stenosis, congenital heart disease, right and left ventricular hypertrophy, myocarditis, and bundle-branch block are the mistaken diagnoses most commonly made. Myocardial infarction, right and left ventricular hypertrophy, and right bundle branch block are the conditions most commonly concealed by the anomalous electrocardiogram.

The most important problems still requiring elucidation are those related to etiology, and to the mechanisms responsible for the abnormal electrocardiogram and paroxysmal rapid heart action.

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ABSTRACTS

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BLOOD COAGULATION

Sawyer, P. N., and Pate, J. W.: Bio-Electric Phenomena as an Etiologic Factor in Intravascular Thrombosis. Am. J. Physiol. **175:** 103 (Oct.), 1953.

In a normal blood vessel the polarity is such that the intima is negative and the adventitia positive. If this is reversed, thrombosis results. The thrombus resembles those formed spontaneously in injured vessels. A current density as small as 0.4 microamperes per square millimeter will create a thrombus in the normal aorta in 4.5 hours. The density of this current is within the physiological limits of injury current across a damaged segment of aorta.

OPPENHEIMER

Jacobsen, B. M.: Effects of Cortisone and Corticotropin on Prolonged Bleeding Time. Arch. Int. Med. **92:** 471 (Oct.), 1953.

Eighteen adults with prolonged bleeding time were treated with cortisone, and one infant was treated with corticotropin. In every instance but one the administration of the drug was followed by a decrease in the bleeding time and by the prevention, or the cessation, of hemorrhage.

BERNSTEIN

Sawyer, P. N., Pate, J. W., and Weldon, C. S.: Relations of Abnormal and Injury Electric Potential Differences to Intravascular Thrombosis. Am. J. Physiol. **175:** 108 (Oct.), 1953.

Minor injury to blood vessels as during dissection renders the intima more negative as compared to the positive adventitia. Transection or severe injury usually makes the intima positive as compared to adventitia. Fresh grafts have a positive intima before and after implantation. Crush injury increased this positive intimal potential difference. Crush injury did not affect the potential difference of freeze-dried grafts. Electrical insulation by polyethylene tubing prevented thrombus formation due to severe injury. Similar pseudo-insulators made of metal do not prevent thrombus formation; the metal is a good conductor. Calculated and observed injury currents in injured and subsequently thrombosed vessels agree well. It is pointed out that these values resemble the current per unit area which causes thrombosis when applied experimentally.

OPPENHEIMER

CONGESTIVE HEART FAILURE

Camara, A. A., Schoch, H. K., Reimer, A., and Newburgh, L. H.: Some Studies of the Mechanism of Intractable Edema. Arch. Int. Med. **92:** 554 (Oct.), 1953.

Data on two normal subjects emphasize again the ability of the organism, when only minimal amounts of sodium are ingested, to conserve sodium by tubular reabsorption of nearly all that was contained in the glomerular filtrate. After this condition had been instituted in one of the normal subjects by sharp restriction of dietary sodium, chloride whose urinary excretion requires a nearly equivalent appearance of total base in the urine, was administered. Less than one-fifth of the base requirement was supplied as sodium. During a second period of ammonium chloride administration while the sodium intake was still restricted, it was found that the urinary sodium was even less. In another healthy subject, following a regimen that caused a marked and rapid depletion of body sodium, the contribution of sodium accompanying the increased urinary excretion of chloride, administered as NH_4Cl, fell to only 2 per cent.

An edematous nephritic patient reacted to the administered chloride by excreting only 20 per cent

of it. This might be explained by the inability of the kidneys to increase production of ammonia and by the small contribution of sodium due to its very efficient reabsorption by the tubules. When tubular reabsorption of sodium was depressed by administration of a mercurial diuretic, the plentiful appearance of sodium in the urine without increase in ammonia was accompanied by a large excretion of chloride. Studies conducted on an edematous patient with heart disease and on two normal subjects showed that under conditions of water restriction, when body water is forcibly lost through evaporation, the anticipated proportionate loss of sodium through the urine did not occur. On the contrary, calculations show that a large transfer of water from the cells into the extracellular space took place in the normal persons. In the edematous patient with heart disease no such transfer was demonstrated. These studies indicate that both the patients with nephritis and those with cardiac disease possessed a very efficient mechanism for the renal tubular reabsorption of sodium. Since in both of the patients the volume of the extracellular fluid was excessive, one is led to conclude that the stimulus which resulted in reabsorption of sodium and water had become greatly increased. The mechanism itself in such patients may be normal and the change be merely quantitative.

BERNSTEIN

CORONARY ARTERY DISEASE

Schnur, S.: Mortality Rates in Acute Myocardial Infarction. II. A Proposed Method for Measuring Quantitatively Severity of Illness on Admission to the Hospital. Ann. Int. Med. **39:** 1018 (Nov.), 1953.

A method was devised to estimate quantitatively the severity of illness of patients with acute myocardial infarction on admission to the hospital. By a predetermined formula, certain specific admission findings and historical data (shock, congestive failure, serious arrhythmias, gallop rhythm, associated serious diseases, history of heart or vascular disease) were assigned a numerical value. This scoring system, termed "Pathologic Index Rating," was found to be closely related to the mortality rate of a large group of patients, ranging from 8 per cent in the group with the lowest rating to 95 per cent in the group with the highest rating. It was felt that this method might be useful in the design of a controlled experiment in which patients could be paired on the basis of their index, and then assigned at random to treated and control groups, rather than the usual method of simple alternation of pairs without regard to severity of illness.

MAXWELL

Ernst, C. E., and Fisch, C.: Medical Intelligence: Subendocardial Infarction. Report of two cases. New England J. Med. **249:** 853 (Nov. 19), 1953.

Two cases with antemortem diagnoses of subendocardial infarction based on the characteristic electrocardiographic findings are presented. In both cases postmortem examination confirmed the diagnosis and showed general narrowing of the coronary vessels without an actual occlusion. The authors postulate that in the presence of an impaired coronary circulation, anemia in the first patient and prolonged vomiting and shock in the second, resulted in subendocardial infarctions. In this form of infarction characteristic Q waves are absent and electrocardiographic changes are limited to R wave and S-T segments. In leads that face the uninjured epicardial surface S-T segment depression is found. Elevation of the S-T segment is found in leads that face the ventricular cavity. These findings must be differentiated from those of "left-sided heart strain" and "digitalis effect."

SAGALL

Chiche, P., Baillet, J., and Verdun de Cantogno, R.: Subendocardial Ischemia of the Left Ventricle and Coronary Insufficiency. Arch. mal. coeur **46:** 865 (Oct.), 1953.

Anatomic, histologic, clinical and electrocardiographic findings are discussed in 42 cases with subendocardial infarction with special reference to the physiology of normal and abnormal coronary circulation. A variety of etiologic groups was represented in the material. Eighteen cases had arteriosclerotic coronary disease but in only 6 was there a thrombotic occlusion of a vessel. In one case a congenital anomaly of the coronary circulation was present. Seven cases had syphilitic aortitis and/or myocarditis. Six cases had valvular disease, four of them pure aortic stenosis and two combined mitral and aortic lesions. There were 10 cases of extracardiac causes of myocardial ischemia such as pulmonary embolism, shock, hemorrhage and arterial hypertension. All had in common chest pain and a more or less characteristic electrocardiographic pattern with S-T depression in the standard and left precordial leads.

Thus coronary arteriosclerosis is a frequent but not invariable cause of interference with coronary circulation. Myocardial infarction is a consequence of its severest acute variety localized to a circumscribed area of the myocardium, whereas subendocardial ischemia and necrosis appear to reflect chronic or subchronic alterations of the coronary flow involving the myocardium of the left ventricle in a more global form. The particular involvement of the subendocardial layer by this type of coronary insufficiency, and the corresponding electrocardiographic pattern are related to the particular distribution of the coronary tree within the ventricular walls and to progressive decline of the pressure gradient across the wall from epicardium to endocardium.

PICK

Goodwin, W. E., and Walter, R. C.: Intra-Aortic Procaine Injection in Aortography. Angiology **4:** 410 (Oct.), 1953.

Intra-aortic injections of 3 to 6 cc. of 1 per cent procaine immediately preceding the injection of contrast media, will partially or completely prevent arterial spasm induced during aortography. The procedure has been used successfully in 25 patients without ill-effects.

WESSLER

Lundbaek, K., and Petersen, V. P.: Lipid Composition of Diabetic and Non-Diabetic Coronary Arteries. Acta med. scandinav. **144:** 354 (Fasc. 5), 1953.

Detailed chemical analysis was performed upon sections of the left coronary artery removed at autopsy from 14 nondiabetic, and 13 diabetic patients of equal average age. The calcium content of the arteries was lower in the group of diabetics than in the group of nondiabetics. Neither the cholesterol nor the total phospholipid content was significantly different in the two groups, nor were the cholesterol–phospholipid ratios importantly different. The lecithin content was lower and the cephalin content was higher in the arteries from the diabetic patients than from the nondiabetic individuals.

ROSENBAUM

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY AND BALLISTOCARDIOGRAPHY

Danzier, G., Durand, M., and Metianu, C.: The Electrocardiogram in Patent Ductus Arteriosus. Arch. mal. coeur **46:** 994 (Nov.), 1953.

The authors present an electrocardiographic study in 52 cases of patent ductus before and following surgery. In 14 cases the tracing was normal, 29 cases showed alterations consistent with left ventricular hypertrophy, usually isolated or combined with right ventricular hypertrophy. In both of the latter two groups there were a few instances with right or left-sided intraventricular conduction defect. Two cases showed only right bundle-branch block. Following surgery there usually was a marked regression of the signs of left ventricular hypertrophy whereas the other alterations did not change much. The clinical significance of the various electrocardiographic patterns in relation to other associated lesions is discussed.

PICK

Scherf, D., and Blumenfeld, S.: Variations of Form of T Waves in Auricular Flutter and Auricular Fibrillation, Associated with Changes of Rate. Am. Heart J. **46:** 543 (Oct.), 1953.

Changes in the form of the T waves in patients with auricular flutter and varying atrioventricular block, as well as in auricular fibrillation, depend mainly on variations of rate. These alterations involve only the terminal phase of the T wave, the RS-T segment remaining unchanged. They are seen mostly in leads V_3, V_4 and V_5. These variations may be present only temporarily, as illustrated in patients with acute myocardial infarction. The changes are attributed to variations in the rate of repolarization in abnormal parts of the myocardium. These may be located even in the subendocardial fibers.

RINZLER

Scher, A. M., Young, A. C., Malmgren, A. L., and Paton, R. R.: Spread of Electrical Activity through the Wall of the Ventricle. Circulation Research **1:** 539 (Nov.), 1953.

The spread of electrical activity through the wall of the ventricle was investigated by means of multipolar recording techniques in open-chested dogs and cats. Multipolar intramural tungsten electrodes permitted recording with a multichannel oscilloscope at very close points within the heart muscle. By constructing isochronous planes in blocks of heart tissue, the direction and speed of cardiac excitation was derived.

Through most of the ventricle, rapid subendocardial activation (average speed: 1.8 meters per second) is followed by slow spread perpendicular to the epicardial and endocardial surfaces (average speed: 300 mm. per second). The rapid subendocardial spread may be via the Purkinje tissue, but this has not been established. The results indicate a syncytial spread of electrical activity. Conduction through the wall is not parallel to muscle fibers nor is it channeled through the individual muscle bundles which make up the tissue. It is not interrupted by connective tissue barriers.

MAXWELL

Alzamora-Castro, V., Abugattas, A., Battilana, G., Rubio, C., Bouroncle, J., Zapata, C., Binder, T., Santa Maria, E., Pando, B., Paredas, D., and Perez, V.: The Fiber Block. An Investigation of Electrocardiographic Alterations Associated with Damage of Myocardial Fibres. Ztschr. Kreislaufforsch. 42: 825 (Nov.), 1953.

On the basis of experimental electrocardiographic studies reported previously, two types of intraventricular block could be distinguished. The first, caused by impairment of conductivity in the specific system, was termed conduction block. The second, caused by slowing of the spread of the impulse through ordinary ventricular muscle fibers, was termed fiber block. The latter type was submitted to further experimental investigation.

Fiber block can be produced by injection of a toxic substance like cocaine or potassium chloride into a coronary artery, or by ligation of a branch of a coronary artery. The resulting electrocardiographic alterations consist in progressive widening of QRS

with secondary T-wave changes. When the damage is very severe, these alterations are associated, or preceded, by S-T deviations with monophasic deformation of the curve. These alterations are focal in type, since it can be shown with the help of direct epicardial leads that they are most marked over the area of maximal damage, and show gradual transitions towards normal, as the electrode is moved away from the area of maximal injury. Toxic and ischemic alterations produced very similar patterns, except that the latter showed (in addition to the changes of ventricular activation) a displacement of the baseline. All observed alterations were only of short duration and resulted either in complete recovery or in death of the involved tissues.

The tracings obtained by this method in the dog are very similar to tracings known to occur in human pathology, e.g.; the severest stages of experimental fiber block resemble initial stages of myocardial infarction, while the tracings obtained with only mild focal damage compare very well with patterns characteristic for heart strain. On the basis of these observations the authors present a new concept for interpretation of various abnormal patterns observed in clinical electrocardiography. They imply various degrees of impairment of the speed of activation and deactivation of the ventricular myocardium caused either by focal (subepicardial or subendocardial) damage, or by through-and-through damage of the entire thickness of the ventricular wall. Theoretic principles are discussed on the basis of which it should be possible to predict an electrocardiographic pattern when the site, the extent, the degree of block, and the position of the electrode are known.

PICK

Tricet, R., Vernant, P., Stamon, A., and Costeas, F.: A Study of the Atriogram in some Types of Congenital Cardiopathies. Arch. mal. coeur **46:** 1024 (Nov.), 1953.

The authors studied the incidence and the type of abnormal P waves in various types of congenital malformations of the heart. The "P congenitale" is a large and pointed triangular wave, usually tallest in lead II, and thus, does not fit the usual criteria of a P mitrale or a P pulmonale, as far as contour and axis deviation are concerned. It is found frequently in congenital heart disease but is not characteristic for any particular lesion. No correlation was found between the occurrence of this type of abnormal P wave and alterations of atrial dynamics found at catheterization, or anatomic lesions of the atria found at autopsy.

PICK

Rosner, S., Newman, W., and Burstein, C. L.: Electrocardiographic Studies during Endotracheal Intubation. VI. Effects during Anesthesia with Thiopental Sodium Combined with a Muscle Relaxant. Anesthesiology **14:** 591 (Nov.), 1953.

Electrocardiograms were recorded on patients before and during endotracheal intubation. Induction of anesthesia was produced by the intravenous injection of 100 to 200 mg. of thiopental sodium in concentrations of 2.5 to 5 per cent. Moderate muscular relaxation was then obtained by the intravenous administration of sufficient doses of various muscle relaxing agents, such as *d*-tubocurarine, dimethyltubocurarine iodide or decamethonium bromide. After allowing three to five minutes for the full effect of the muscle relaxant, laryngoscopy was attempted. Laryngospasm occurred in about one-third of the cases. Patients requiring the additional employment of supplementary anesthesia for successful intubation were discarded from this series. In all, 76 patients were studied. In 60 per cent of the patients (46 cases) sinus tachycardia varying from 100 to 150 beats per minute was induced by intubation. In one case additional arrhythmias recorded were occasional ventricular contractions (two cases), nodal rhythm (one case), ventricular tachycardia (one case) and bigeminal ventricular tachycardia (one case). All the episodes of arrhythmia were transient and disappeared with adequate oxygenation. With easy performance of intubations arrhythmias were not induced. To avoid cardiac complications during intubations any decreased pulmonary exchanges produced by thiopental sodium should be compensated for by manual assistance of respiration and adequate oxygen.

SAGALL

Rahm, W. E., Jr., Barmore, J. L., Ellestad, I. M., and Dunn, F. L.: Local and Long-Distance Transmission and Storage of Electrocardiograms and Other Low-Frequency Signals. Circulation Research **1:** 518 (Nov.), 1953.

A procedure using frequency modulation was described which permitted transmission of electrocardiograms and electroencephalograms over available local and long-distance telephone facilities. Successful transmission was reliably accomplished over a wide variety of telephone lines in a multiplicity of combinations. Frequency modulation permits the design of standardized transmitting and receiving equipment and thus simplifies the problem of local and long-distance transmission of low-frequency signals.

MAXWELL

ENDOCRINE EFFECTS ON CIRCULATION

West, G. B., Shepherd, D. M., Hunter, R. B., and Macgregor, A. R.: The Function of the Organs of Zuckerkandl. Clin. Sc. **12:** 317 (Nov.), 1953.

The organs of Zuckerkandl comprise a mass of paraganglia situated along the aorta near the origin of the inferior mesenteric artery. These organs are

found in the human fetus and reach their maximum development in early life. It has been known that extracts from these organs have vasoconstrictor action, and that tumors of these organs represent a majority of extra-suprarenal chromaffin tumors.

The authors studied the histology and the pressor amine content of the adrenal medulla and the organs of Zuckerkandl in nearly 100 children. They found that the organs of Zuckerkandl develop earlier than the adrenal medulla, and that at birth they contain more pressor amines than the adrenal medulla. At this time the organs of Zuckerkandl contain only noradrenaline. During the first year of life there is a decline in pressor amine activity in these organs, accompanied by structural changes of involution. At the same time the adrenal medulla is rapidly maturing, and adrenaline appears in both types of organs. By the third year of life, the organs of Zuckerkandl are quite fibrotic, and only a trace of pressor activity remains.

The authors conclude that it is very probable that the organs of Zuckerkandl supply a potent pressor amine to the body and help maintain blood pressure in the fetus and young infant. During infancy this function is gradually taken over by the adrenal medulla, as the organs of Zuckerkandl atrophy.

ENSELBERG

HYPERTENSION

Olsen, N. S.: Oxidative Metabolism of Normotensive and Hypertensive Rat Tissues. Am. J. Physiol. **175:** 129 (Oct.), 1953.

Broken cell preparations from the constricted kidney of a hypertensive rat had a much smaller oxygen uptake than its contralateral kidney. The uptake of the constricted kidney was increased by vitamin B_6. Oxidation of amino acids and amines was depressed by preparation of the constricted kidney. Pyridoxal did not appreciably affect these oxidations.

OPPENHEIMER

Meneely, G. R., Tucker, R. G., Darby, W. J., and Auerbach, S. H.: Chronic Sodium Chloride Toxicity: Hypertension, Renal and Vascular Lesions. Ann. Int. Med. **39:** 991 (Nov.), 1953.

In view of the lack of information on the chronic effects of dietary sodium chloride, a long-term study was undertaken in male albino rats. Diets with varying salt content (0.01 to 9.8 per cent) were fed at will from the age of 5 weeks.

Water consumption was related directly to the amount of salt in the diet, and diets both high and low in salt reduced the rate of growth. Sustained arterial hypertension occurred in the rats eating high levels of sodium chloride, with edema and a nephrotic-like syndrome developing in 18 per cent of these animals. Pathologic lesions were observed in the kidneys and to a lesser extent in other organs of rats on the high-salt diet. The authors point out some of the similarities to human hypertension but emphasize the need for further study before drawing any definite conclusions.

MAXWELL

Wilkins, R. W., Tinsley, C. M., Culbertson, J. W., Burrows, B. A., Judson, W. E., and Burnett, C. H.: The Effects of Venous Congestion of the Limbs upon Renal Clearances and the Excretion of Water and Salt. I. Studies in Normal Subjects and in Hypertensive Patients before and after Splanchnicectomy. J. Clin. Investigation **32:** 1101 (Nov.), 1953.

In this detailed study a number of findings are presented. In general, the effects of venous congestion of the limbs upon renal clearances and the excretion of salt and water are essentially similar in normotensives and in hypotensive patients before and after splanchnicectomy. Characteristically, about 10 minutes after congestion of the limb, the urine flow decreases and frequently falls to one-tenth its previous rate. There is an accompanying decrease in renal plasma flow, filtration rate, and sodium, chloride, and potassium excretion. The decrease in electrolytes and clearance substances was not as great as that of water, so that the concentration of these materials in the urine usually rose. It is reasonable to suppose that the renal responses to venous congestion of the limbs are integral parts of homeostatic mechanisms for counteracting the effect of an inadequate circulating blood volume. Just what causes salt and water retention as a result of a decrease in effective circulating blood volume is, at the moment, unknown. Changes in venous, right atrial, right ventricular, or pulmonary arterial pressures do not seem to be likely possibilities. Neither do stimuli such as discomfort, venous distention or loss of fluid locally appear to be responsible. Furthermore, it appears that these effector mechanisms are not dependent upon the splanchnic sympathetic nervous system since, as this paper shows, the responses occur similarly in splanchnicectomized hypertensives as well as in normotensive or unoperated hypertensive subjects. It would appear that these mechanisms are mediated at least in part through humoral or local renal mechanisms. Among these may be considered the posterior pituitary antidiuretic hormone and the adrenocortical hormone.

WAIFE

Dewar, H. A., Owen, S. G., and Jenkins, A. R.: Effects of Hexamethonium Bromide on the Cerebral Circulation in Hypertension. Brit. M. J. **2:** 1017, (Nov. 7), 1953.

In six patients mean arterial blood pressure fell by an average of 30 per cent but no change in mean cerebral blood flow occurred. The mechanism of the

fall in cerebral vascular resistance with fall in blood pressure is unexplained.

McKusick

Ford, R. V., Moyer, J. H., and Spurr, C. L.: Hexamethonium in the Chronic Treatment of Hypertension—Its Effects on Renal Hemodynamics and on the Excretion of Water and Electrolytes. J. Clin. Investigation **32:** 1133 (Nov.), 1953.

Hexamethonium in hypertensives led to a reduction in blood pressure without a reduction in renal plasma flow, glomerular filtration, or tubular excretory capacity with the subject in the supine position. In the ambulatory group, there was a depression of glomerular filtration, renal plasma flow, and Tm para-aminohippurate due to vasoconstriction before hexamethonium therapy. Following the use of this drug there was a further drop in pressure and a reduction in renal functions which was often more marked than in the untreated patient. Ambulation after hexamethonium is accompanied by a decrease in the excretion of sodium, potassium, and water. Although renal functions are depressed, there is a return to control values during recumbency even though the blood pressure remains reduced. It would seem that this period of recumbency may also allow for the necessary homeostatic balances or compensations to prevent retention of renal excretory products such as urea nitrogen.

Waife

Gordon, D. B., Drury, D. R., and Schapiro, S.: The Salt-Fed Animal as a Test Object for Pressor Substances in the Blood of Hypertensive Animals. Am. J. Physiol. **175:** 123 (Oct.), 1953.

Cross transfusion from renal hypertensive rabbits into recipients on a regimen of 2 per cent sodium chloride drinking water produced an elevated blood pressure in the recipients. Similar transfusions into normotensive animals who were not receiving salt were without effect. When blood from normotensive rabbits was given to animals on the salt regime no rise or only very small elevations were observed.

Oppenheimer

Rønnov-Jessen, V.: Exercise Tests during Treatment of Hypertension with Hexamethonium. Lancet **2:** 706 (Oct. 3), 1953.

The author states that occasional patients may develop symptoms of hypotension during and after exercise even though the blood pressure in the upright position has been only slightly reduced. This peculiarity can be recognized and appropriate regulation of dosage accomplished, if the blood pressure during exercise is determined in the treated patient.

McKusick

Mendlowitz, M.: The Treatment of Hypertension with Drugs. Ann. Int. Med. **39:** 999 (Nov.), 1953.

Current theories of the humoral and neurogenic factors in the genesis of hypertension are reviewed. Since most therapy is directed at the neurogenic factor, the various nervous pathways which influence sympathetic vasomotor tone are diagrammed. Drugs are grouped according to their site of action, with discussion of their relative merits, side-effects, doses, and contraindications.

At the cortical level, barbiturates are the most useful drugs, although these may be replaced eventually by Rauwolfia serpentina. At the hypothalamic level, 1-hydrazinophthalazine and protoveratrine are the most effective; whereas at the ganglionic level hexamethonium bromide or chloride is the drug of choice. Block of sympathetic nerve endings, smooth muscle or of capillaries is at present of minimal practical value in the treatment of hypertension. Salt depletion by diet and dietary adjuvants appear to affect the non-neurogenic or intrinsic factors in hypertension. Sympathectomy should be reserved for patients with a large neurogenic element who fail to respond to adequate medical therapy. The treatment of hypertension should be undertaken only when that disease under observation represents a hazard to a patient's life or health.

Maxwell

Goldblatt, H., Lamfrom, H., and Hass, E.: Physiological Properties of Renin and Hypertensin. Am. J. Physiol. **175:** 75 (Oct.), 1953.

In the dog, rise in blood pressure is proportional to the injected intravenous dose of renin and may be used as a method of assay. A more complex indirect method for the assay of hypertensin is described. Anesthesia reduces the sensitivity to renin and hypertensin. Tachyphylaxis to renin does not occur if the blood pressure is allowed to return to normal between doses. To secure a sustained elevation in blood pressure with renin the supply of hypertensinogen must be adequate and the conditions of the arterioles must be such that they are capable of adequate response to more hypertensin. Half of an intravenous dose of 250 U of renin disappears from the blood in 10 minutes and not more than 3 per cent remains in one hour. The fate of this substance is not known.

Oppenheimer

PATHOLOGIC PHYSIOLOGY

Bickford, R. H., and Duff, R. S.: Influence of Ultrasonic Irradiation on Temperature and Blood Flow in Human Skeletal Muscle. Circulation Research **1:** 534 (Nov.), 1953.

The local circulatory effects of ultrasonic irradiation of the upper limbs were studied under con-

trolled conditions by venous occlusion plethysmography. A consistent, sustained increase in flow occurred only with high intensities (over 3.0 watts per square centimeter) of ultrasonation; with more tolerable ultrasonic intensities (2.0 watts per square centimeter), vasodilatation was inconstant. Ultrasonic irradiation of the extremities at tolerable levels of intensity is not an effective means of promoting a sustained increase in blood flow. Such vasodilatation as occurs seems to result from heating of the deep tissues and may be produced more efficiently by other simpler measures.

MAXWELL

Goodale, W. T., and Hackel, D. B.: Measurement of Coronary Blood Flow in Dogs and Man from Rate of Myocardial Nitrous Oxide Desaturation. Circulation Research **1:** 511 (Nov.), 1953.

A technic of measuring left ventricular coronary blood flow in dogs and man from the rate of myocardial nitrous oxide desaturation is presented. After saturating the subjects with 15 per cent nitrous oxide, a series of one-minute integrated samples is drawn continuously and simultaneously from arterial and coronary venous catheters during the first few minutes of breathing room air. The curves and values obtained are closely similar to values obtained by an immediately preceding observation of the rate of saturation, an accepted technic. The desaturation method is, therefore, considered valid, and affords several technical advantages over the saturation method. The coronary blood flow in resting normal man averaged 96 cc. per 100 Gm. of left ventricle per minute.

MAXWELL

Kitchin, A. H., Sanger, C., de Wardener, H. E., and Young, I. M.: The Blood Flow in Human Muscle during Cyclopropane Anesthesia. Clin. Sc. **12:** 361 (Nov.), 1953.

It is known that during the first hour of light anesthesia there is an increase in muscle blood flow. The authors studied forearm blood flow during cyclopropane anesthesia in seven patients undergoing varicose vein ligations. They found a mean increase of 82 per cent in forearm flow during light anesthesia. However, in the contralateral limb, which had been subjected to nerve block, there was no increase in flow.

During deep anesthesia, blood flow was reduced in both the normal and the nerve-blocked forearms by about 40 per cent. When the anesthesia was lightened, blood flow increased again. These changes in flow were not related to changes in arterial blood pressure, oxygen concentration, or alveolar carbon dioxide concentration. The authors conclude that the vasodilatation occurring during light anesthesia is dependent upon an intact nervous supply. On the other hand, the vasoconstriction of deep anesthesia is probably due to a direct response of blood vessels to increased concentration of cyclopropane, or to the release of a vasoconstrictor substance.

ENSELBERG

Prinzmetal, M., Goldman, A., Gerlach, E., and Kennamer, R.: Nature of Spontaneous Auricular Flutter in Man. J.A.M.A. **153:** 553 (Oct. 10), 1953.

High speed, color cinematographs of the exposed auricles in a patient with auricular flutter were recorded simultaneously with limb lead electrocardiograms during mitral commissurotomy. It was clearly shown that the left and right auricular appendixes contracted simultaneously. This observation is entirely incompatible with the circus movement theory. In this case electrocardiographic limb leads showed inverted auricular depolarization waves followed by upright repolarization waves. Such complexes occur when the ectopic focus is in the caudal region of the auricles distant from the sinoauricular node. This is a common type of clinical auricular flutter while the rare type arises from a cephalic focus. In all instances, the flutter wave travels away from the ectopic focus until it terminates at the opposite extremity. No circus movement occurs in the spontaneously fluttering auricles of man.

KITCHELL

Kramár, J.: Stress and Capillary Resistance (Capillary Fragility). Am. J. Physiol. **175:** 69 (Oct.), 1953.

Stress was produced by forced exercise or exposure to cold. Capillary resistance is first increased and then critically decreased. After this resistance is very low, but is then restored to normal. The author refers to the critical fall and low resistance which follows as the "capillary crisis." Shaw adrenalectomy and ether anesthesia produced similar responses. Some variations of the fundamental pattern exist. The type of stress has no influence but intensity of stress, diet and individual characteristics do contribute to the capillary response. The opinion is expressed that the early rise may be due to ACTH cortisone mechanisms, the crisis being the result of decreased adrenal cortical activity which is independent of anterior pituitary activity.

OPPENHEIMER

Farber, S. J., and Eichna, L. W.: An Intracardiac Catheter with Inflatable Balloon for Producing Increased Venous Pressures in the Venae Cavae of Man. J. Clin. Investigation **32:** 1140 (Nov.), 1953.

This paper describes a double-lumen, intracardiac catheter equipped with a rubber balloon at the proximal opening. It can produce venous pressures up to 250 mm. of water in the superior and inferior

venae cavae of man. No significant untoward effects were noted in 49 patients.

WAIFE

Gray, F. D., Jr., and Gray, F. G.: Some Factors Influencing the "Pulmonary Capillary" Pressure Curves Obtained by Means of a Cardiac Catheter. Angiology **4:** 436 (Oct.), 1953.

"Pulmonary capillary" pressure curves were obtained from 31 of 49 patients with mitral valve disease, congenital and other heart diseases, and chronic pulmonary disease. Difficulties in the interpretation of the curves were due to artefacts in the catheter technic and the complications caused by hemodynamic factors responsible for the production of the pressure waves themselves. The height and shape of the curve appear to be of value in the diagnosis of mitral stenosis. The authors conclude that the technic requires further evaluation.

WESSLER

Bjork, V. O., Malmstrom, G., and Uggla, L. G.: Left Auricular Pressure Measurements in Man. Ann. Surg. **138:** 718 (Nov.), 1953.

The estimation of the amount of regurgitation through the stenosed mitral valve is of great importance, and may not be accurately made by known clinical methods. Indirect methods to evaluate the degree of insufficiency by electrokymography and heart catheterization include so far too many unknown factors to be conclusive. The pulmonary capillary pressure curve has been ascribed the most significant value.

Additional indirect methods of determining the left auricular pressure curve have been developed. They are: puncture of the left auricle through the left main bronchus during bronchoscopy and the obtaining of pressure measurements in the left auricle through the esophagus via an esophagoscope.

Because both of these methods are tiresome and uncomfortable for the patient, the authors have developed direct methods for obtaining these curves. These involved an anterior approach where the needle may be introduced through the anterior chest wall through the left ventricle into the left auricle. The posterior approach has been explored by one of the authors during intrathoracic surgery. This approach may be made from the left side or from the right side; this method was employed in nine cases. Simultaneous pressure measurements in the pulmonary capillaries and in the left auricle have been performed in one case with normal mitral valves and in six cases with mitral stenosis with a varying degree of regurgitation.

The pressure curve in the pulmonary capillaries closely reflects the pulse pattern in the left auricle in most cases. It is postulated that the left auricular pressure curve might be a good method in evaluating the degree of insufficiency complicating a case with mitral stenosis.

DENNISON

Luft, R., and Von Euler, U. S.: Two Cases of Postural Hypotension Showing a Deficiency in Release of Norepinephrine and Epinephrine. J. Clin. Investigation **32:** 1065 (Nov.), 1953.

In two typical cases of postural hypotension, it was found that daily excretion of epinephrine and norepinephrine was low. This may be connected to the inability of the sympathetic nervous system to react to postural changes. The subcutaneous administration of norepinephrine relieved the signs of low blood pressure. The normally occurring increase in excretion of epinephrine after insulin administration was lacking in these patients. Furthermore, the pulse rate and blood pressure did not show the typical changes of epinephrine activity during insulin hypoglycemia, and the hypoglycemic symptoms were different from those observed in healthy subjects. In one subject, infused norepinephrine was excreted normally. There was also a complete refractoriness to histamine in regards to subjective signs and epinephrine excretion. There did seem to be evidence that there was a decreased ability of the adrenal medulla to release epinephrine on direct stimulation.

WAIFE

Farber, S. J., Becker, W. H., and Eichna, L. W.: Electrolyte and Water Excretions and Renal Hemodynamics during Induced Congestion of the Superior and Inferior Vena Cava of Man. J. Clin. Investigation **32:** 1145 (Nov.), 1953.

Using the intracardiac catheter previously described, detailed studies of the effects of elevated vena caval pressures were performed. Essentially similar changes in excretions and hemodynamic and blood pressure changes occurred when the obstruction was produced in the inferior vena cava above the renal veins, below renal veins, and in the superior vena cava. The findings were as follows: the urinary excretion of sodium and chloride and, less consistently, of potassium and water were decreased. This excretion was usually due to reduced water excretion because the urinary electrolyte concentrations tended to remain unchanged. There was a decrease of about 15 to 25 per cent in renal plasma flow and glomerular filtration rate at the onset of venous congestion. As the congestion was maintained, the hemodynamic functions improved and were returning to control values while the water and electrolyte excretions remained reduced. The systolic and pulse pressures fell slightly; the diastolic and mean pressures remained essentially unchanged. There were no effects noted on heart rate or in the electrocardiogram. Following release of the inferior vena caval congestion, the various determinations

returned to normal levels within thirty minutes. However, following release of superior vena caval congestion, the water and electrolyte excretions returned very slowly, or not at all at 30 minutes, whereas the renal hemodynamic changes promptly returned to control values.

WAIFE

Fitzhugh, F. W., Jr., McWhorter, R. L., Jr., Estes, E. H., Jr., Warren, J. V., and Merrill, A. J.: The Effect of Application of Tourniquets to the Legs on Cardiac Output and Renal Function in Normal Human Subjects. J. Clin. Investigation **32:** 1163 (Nov.), 1953.

This study was an investigation of the pathogenesis of the renal function changes that occur when blood is pooled in the lower extremities by the use of tourniquets. A significant but small fall in cardiac output was noted. There were highly significant falls in the effective plasma flow, urine flow, and sodium excretion. The fall in glomerular filtration rate was of borderline significance. All these functions returned to normal upon release of the tourniquets, although the return occurred at different rates. The decrease in cardiac output is probably due to a diminished effective blood volume. The reduced output, in turn, leads to a fall in renal plasma flow. It is interesting that the observed changes in renal function are similar to those in other conditions with diminished cardiac output, such as chronic congestive heart failure and shock. Sodium retention probably was due to increased tubular reabsorption. The authors noted an antidiuresis after the application of tourniquets and suggest that this may be due to increased activity of the posterior pituitary resulting from the diminished effective blood volume.

WAIFE

PATHOLOGY

Rosenbaum, H. D., Nadas, A. S., and Neuhauser, E. B. D.: Primary Myocardial Disease In Infancy and Childhood. Am. J. Dis. Children. **86:** 28 (July), 1953.

Forty-five infants and children with a syndrome of myocardial disease characterized by cardiomegaly, absence of significant murmurs, electrocardiographic abnormalities and normal blood pressure have been studied. The following pathologic processes were found in 26 of these patients who came to autopsy: (1) glycogen-storage disease of the heart (three patients); (2) aberrant left coronary artery (one patient); (3) medial necrosis of the coronary arteries (two patients); (4) idiopathic myocarditis (10 patients), and (5) subendocardial sclerosis (10 patients). An attempt has been made to establish clinical criteria for the differential diagnosis of these five separate diseases in living patients. All of these patients showed marked generalized cardiomegaly by x-ray, and the vast majority demonstrated left ventricular hypertrophy and T-wave changes of myocardial damage by electrocardiography. The value of digitalis in the treatment of some of these patients is stressed.

BERNSTEIN

McKeown, F.: The Left Auricular Appendage in Mitral Stenosis. Brit. Heart J. **15:** 433 (Oct.), 1953.

The author studied the histologic appearance of 53 appendages removed during mitral valvotomy and that of 92 taken from hearts with mitral stenosis on the postmortem files in her hospital in an attempt (1) to identify the different phases of evolution of the endocardial nodule present in the biopsy specimens and (2) to investigate the incidence and relationship between active rheumatic lesions in the appendage and in other regions of the heart.

The entire life cycle of the Aschoff nodule could be reconstructed from the appearances in these specimens. Seventeen of the 92 examined from the necropsy specimens were likewise positive. All of these showed lesions that were similar and in the same phase as those seen in the ventricle. Five others were positive only in the ventricular muscle.

It is felt that active carditis in valvotomy patients may constitute a hazard and may precipitate or contribute in some measure to a fatal outcome. It is even possible that in the period before operation it may be one of the factors responsible for the aggravation of symptoms that renders operative treatment necessary.

SOLOFF

Grant, R. P.: Architectonics of the Heart. Am. Heart J. **46:** 405 (Sept.), 1953.

The author indicates that the advent of newer diagnostic and therapeutic technics for heart disease has necessitated that the clinician understand the functioning or three-dimensional architecture of the heart and the changes in this architecture which take place with heart disease. A method is described for studying at necropsy the three-dimensional structure of the heart. The clinical findings in 60 selected normal and abnormal hearts are presented.

In the normal heart, the left ventricle has a relatively horizontal position in the body with its mitral and aortic orifices facing the right side of the body. The aorta makes a nearly 90 degree angle with the direction of the outflow tract of the left ventricle before it emerges from the pericardium. The right ventricle lies altogether anteriorly to the left ventricle; and the septum, which is parallel with the frontal plane of the body, is intrinsically a part of the left ventricle rather than an independent muscular partition between the two ventricles.

The sequences of change in the course of development of right ventricular hypertrophy and dilatation are described. An anatomic explanation is

offered for the nearly invariable occurrence of right ventricular hypertrophy whenever left ventricular hypertrophy is marked.

An aspect of the pathology of mitral stenosis which has not been widely appreciated is the shortening of the posterior wall of the left ventricle. The implications of this shortening for the development of mitral insufficiency are discussed, and a striking example is presented in detail. The shortening of the posterior wall is believed to represent atrophy of this region of the left ventricle due to the immobilizing effect of the rigid mitral valve elements. It is pointed out that the shortening of the chordae tendineae of mitral stenosis is more apparent than real.

The architectural changes in left ventricular hypertrophy are described. It was found that the hypertrophy tends to be circumferentially symmetric, with the septum participating equally with other regions in the hypertrophy. When the hypertrophy is marked the distal part of the outflow tract of the left ventricle is converted into a narrow conus aorticum, and evidence is offered that occasionally this narrowing may produce turbulence and obstruction to outflow from the left ventricle. The pathologic basis for the Bernheim syndrome is examined and it is shown that the method of dissection used by Bernheim and his followers was inadequate for demonstrating obstruction of the right ventricular outflow tract. No instance of right ventricular outflow obstruction due to left ventricular hypertrophy was encountered among the hearts examined, and the existence of this syndrome is questioned. The three-dimensional changes which take place with left ventricular dilatation are described, and the role of elongation of the mitral valve elements in left ventricular hypertrophy and in dilatation is discussed.

RINZLER

PHARMACOLOGY

Wannamaker, L. W., Denny, F. W., Perry, W. D., Rammelkamp, C. H., Jr., Eckhardt, G. C., Houser, H. B., and Hahn, E. O.: The Effect of Penicillin Prophylaxis on Streptococcal Disease Rates and the Carrier State. New England J. Med. **249:** 1 (July 2), 1953.

In pilot studies to determine the effect of penicillin on the carrier state, it was observed that an oral dose of one million units twice daily for 10 days was almost always effective in eliminating the carrier state. Half of this dose for the same period was probably also effective. A dose of one million units orally, twice daily for only five days, failed to eradicate the carrier state in 45 per cent of the carriers. A dose of only 250,000 units once daily for 10 days failed in many instances. A single intramuscular dose of 600,000 units of procaine penicillin in oil failed to eradicate Group A streptococci, but this same dose given every other day for a total of four doses was almost always effective. The carrier state was eliminated in all of 10 men who were given a total of 1,800,000 units of benzethacil (dibenzylethylenediamine penicillin G) in two simultaneous injections. A single dose of 600,000 units was effective in 90 per cent of the carriers studied. All strains of Streptococci isolated were sensitive to 0.05 units or less of penicillin and no increased resistance was found in the strains isolated after administration of the drug. It was observed that the failures encountered, especially with the more successful regimes, tended to occur in the nasal carriers.

A large-scale prophylactic study was carried out on entire squadrons of men with administration of one million units of penicillin orally twice daily for either five or ten days. The streptococcal disease rates and carrier rates were definitely reduced in those men who received penicillin. Three weeks after the drug was discontinued the streptococcal disease rate was the same in the treated group as in those who had served as controls.

The incidence of reactions was low. One per cent of the treated group had definite skin reactions, and another group of similar size had possible reactions. Of a sample group of 169 men, 60 per cent had loose stools during the period of drug administration. The only serious reaction was a single instance of moderate laryngeal edema.

ROSENBAUM

Fong, T. C.: Oral Metrazol in Psychoses with Cerebral Arteriosclerosis. J. Am. Geriatrics Soc. **1:** 662 (Sept.), 1953.

Metrazol was given orally for 180 days to 35 patients (14 female and 21 male) with a diagnosis of psychosis with cerebral arteriosclerosis. The average age was 77 years. The length of illness varied from six months to nineteen years. During the first week 0.1 Gm. was given four times daily. During the second week this was increased to 0.2 Gms. four times daily and was there maintained in the majority of patients. A few patients needed 0.3 Gm. four times daily. At this dose level, some developed mild nausea and vomiting.

Improvements which occurred in sixteen patients, consisted of a decrease in anxiety, agitation, emotional lability, fatigability and irritability, together with better sleep habits and appetites.

Five patients died during the study. In none was Metrazol a contributing factor.

RINZLER

Wright, S. S., Purcell, E. M., Kass, E. H., and Finland, M.: Penicillin G and Benzethacil by Mouth: Comparison of Penicillin Levels in Plasma of Normal Men after Single Oral Doses. J. Lab. & Clin. Med. **42:** 417 (Sept.), 1953.

The levels of penicillin in the blood plasma were determined in the same 12 subjects after administration of single doses of 200,000 units of tablets of

buffered and unbuffered potassium penicillin G and as benzethacil ("Bicillin") in three types of tablets having different disintegration times, before and after breakfast.

The most uniformly absorbed among these preparations was the tablet of potassium penicillin buffered with sodium citrate. This preparation yielded the highest peak levels, and its absorption was not significantly affected by the meal. The unbuffered tablet of potassium penicillin G yielded lower average levels of penicillin in the plasma, and these were further reduced and somewhat irregular when the dose was given after breakfast. Bicillin in the "hard" tablet was slow to disintegrate and was absorbed very erratically. Bicillin was slow to appear in the plasma and the levels rose irregularly, but higher peaks were reached in some subjects when the tablet was given after breakfast. Benzethacil tablets which disintegrated more quickly yielded higher peak concentrations of penicillin, and these were achieved more rapidly and were sustained if given after the meal. The levels obtained with this preparation were intermediate between those resulting from potassium G and those following the ingestion of the hard tablet of bicillin.

There were no cumulative effects on the penicillin levels in the plasma following seven daily doses of either the buffered penicillin G or the benzethacil, each given after breakfast.

The most reliable and most desirable of the preparations tested from the viewpoint of absorption were the buffered tablets of potassium penicillin G.

MINTZ

Root, M. A.: Comparison of the in Vivo Sodium-Removing Activity of Various Types of Ion Exchange Resins in Rats. J. Lab. & Clin. Med. **42:** 430 (Sept.), 1953.

Two carboxylic acid exchange resins, Amberlite XE-112 and Amberlite XE-103, were found to have two to three times the sodium binding capacity of Amberlite XE-64 (the standard material), in vivo experiments in rats.

None of the sulfonic cation exchange resins tested had the ability to bind sodium in vivo as effectively as did the carboxylic acid resins XE-112 and XE-103. In fact none of the sulfonic acid resins tested was any more efficient in binding sodium than was Amberlite XE-64. Unless other sulfonic acid resins can be developed with higher in vivo capacities for binding sodium, it is not necessary to submit patients to the greater acidity of the sulfonic acid type resin in order to obtain maximum sodium binding.

Two phosphonic acid cation exchange resins were less than one-half as efficient as Amberlite XE-64, in binding sodium in the gastrointestinal tract of the rat. The addition of anion to the cation exchange resin fed rats did not enhance the sodium binding ability of the cation resin. Liquid resins are impractical for clinical use because of the great bulk of liquid which would have to be ingested in order to remove any appreciable amount of sodium.

The higher the dietary intake of sodium, the greater was the amount of sodium bound per gram of resin, but the lower was the percentage of ingested resin that was excreted in the feces. This finding emphasizes the necessity of keeping the sodium intake low, if there is a desire to decrease the absorption of sodium from the gastrointestinal tract.

MINTZ

Eisenberg, H., and Brandfonbrener, M.: Observations on Penicillin-Treated Cardiovascular Syphilis: 1. Uncomplicated Aortitis. Am. J. Syph. **37:** 439 (Sept.), 1953.

Forty-three cases diagnosed as uncomplicated syphilitic aortitis which met rigid diagnostic criteria are presented. All patients were asymptomatic. They were treated with various doses of penicillin and followed from six months to five years. No untoward reactions were observed during treatment or in subsequent follow-up. To discuss its effectiveness, a longer follow-up will be necessary, but thus far no progression or regression of the disease has been noted. Histopathologic reports should reveal the ultimate result of penicillin treatment as well as the amount of treatment needed to heal the syphilitic process in the aorta.

BERNSTEIN

Eisenberg, H., and Brandfonbrener, M.: Observations on the Penicillin Treatment of Cardiovascular Syphilis. II. Complicated Aortitis. Am. J. Syph. **37:** 442 (Sept.) 1953.

Of 178 untreated patients with complicated aortitis, only one had a negative serologic test for syphilis. Eleven patients having syphilitic saccular aneurysm had normal blood pressures. Thirty per cent of patients with complicated aortitis also had neurosyphilis.

Sixty-three per cent of symptomatic penicillin-treated patients with syphilitic aortic insufficiency noted subjective improvement. The death rate, during the observation period, in patients with complicated syphilitic aortitis was greater among symptomatic patients (21 per cent) than among asymptomatic patients (5 per cent). The death rate of penicillin-treated patients with complicated syphilitic aortitis is high, but no suitable control group is available for determining the significance of this observation. Once severe anatomic and resultant functional changes have occurred, no dramatic decrease in death rate can be expected. The lower death rate among asymptomatic cases may be an argument for administration of treatment as early as possible, provided it can be shown that treatment prevents progression to the symptomatic phase.

BERNSTEIN

Russek, H., Urbach, K., Doerner, A., and Zohman, B.: Choice of a Coronary Vasodilator Drug in Clinical Practice. J.A.M.A. **153:** 207 (Sept. 19), 1953.

Because of erroneous impressions of coronary vasodilator action gained through pharmacologic tests on animals, from performance in uncontrolled studies in human disease, and from carefully controlled analyses of the subjective sensation of pain in patients with angina pectoris, the authors have used a new method of evaluation of such drugs. They used a group of carefully selected persons who had reproducible electrocardiographic responses to standard exercise tests (Master two-step test). Fifty-two such patients qualified in a screening of 3,000 patients with coronary artery disease. The following conclusions were reached by tests: (1) Glyceryl trinitrate (nitroglycerin) in therapeutic doses exerts a strikingly favorable effect on the response to exercise as recorded electrocardiographically. (2) Papaverine in the dosage of 1 to 2 grains (0.065 to 0.12 Gm.) intravenously or 3 to 8 grains (0.194 to 0.518 Gm.) orally is effective in some patients. Benefit was not, however, observed with the usual therapeutic doses of the drug. (3) Of all the agents tested, pentaerythritol (Peritrate) tetranitrate appears to be the most effective drug currently available for prolonged prophylactic therapy in angina pectoris. (4) Aminophylline, Roniacol, Priscoline, tetraethyl ammonium chloride, octyl nitrite, dioxyline phosphate, visammin, heparin, and bishydroxycoumarin appeared unimpressive when evaluated according to this method. (5) Ethyl alcohol consistently failed to influence the electrocardiographic response to exercise although it prevented or reduced the severity of anginal pain. Alcohol should be recognized as a rapidly acting sedative and should no longer be regarded as a coronary vasodilator drug. Morphine is identical to alcohol in its effect. (6) Of the drugs tested only glyceryl trinitrate, papaverine, and pentaerythritol tetranitrate appear worthy of continued clinical use as vasodilators in the management of angina pectoris.

KITCHELL

Voyles, C., Sieber, H., and Orgain, E.: Ethaverine in the Treatment of Angina Pectoris. J.A.M.A. **153:** 12 (Sept. 5), 1953.

A "double-blind" experiment was performed using Ethaverine to avoid the common errors of physician enthusiasm, new drug psychologic effect on the patient, and the spontaneous variations in angina pectoris. In a group of 22 patients under therapy with Ethaverine alternating with placebo over periods of 12 weeks, this drug was found to be no more effective in reducing either the severity or frequency of angina pectoris than similar amounts of lactose given under the "double-blind" conditions.

KITCHELL

Simpson, J. H., Hall, M., and Morgan, B.: Polyarteritis Nodosa Treated with ACTH. Report of a Case, with Recovery. Brit. Med. J. **7:** 659 (Sept. 19), 1953.

A 15 year old boy was admitted to the hospital because of recurrent purpura, three weeks' persistent fever, weight loss, and pain in the upper arms, thighs, and calves. Laboratory studies revealed anemia, elevated sedimentation rate, albuminuria, and hematuria. Pathologic examination of a biopsy specimen obtained from tender subcutaneous nodules which appeared during the first week after admission revealed findings characteristic of the acute arteritis and periarteritis of polyarteritis nodosa. Treatment with corticotropin (ACTH) was instituted. The initial dose was 15 mg. every six hours for three weeks. This was reduced to 15 mg. every 12 hours for an additional three months and then to 15 mg. daily for one week following which it was omitted. The patient showed immediate subjective improvement, disappearance of the subcutaneous nodules, and a weight gain. Fever subsided in three weeks. Hematuria, sedimentation rate and blood pressure gradually diminished to normal. During the sixteen month follow-up period since discharge from the hospital there has been complete remission of the disease process.

SAGALL

Calenda, D. G., Uriccho, J. F., and Friedman, L. M.: The Management of the Shock in Myocardial Infarction with *L*-Norepinephrine. Am. J. M. Sc. **226:** 399 (Oct.), 1953.

A group of 13 patients developed the shock syndrome following an acute myocardial infarction proven by electrocardiogram. Each of them received Levophed in the management of cardiogenic shock. The solution was prepared in the conventional fashion by adding 4.0 mg. of Levophed to 1000 cc. of 5 per cent dextrose in water. The rate of administration was determined by the pressor response obtained. Of the 13 patients, 2 experienced a significant pressor response, however, only four of them survived. The authors concluded that the mortality rate of shock accompanying myocardial infarction was not significantly reduced by the use of this drug.

SHUMAN

Bresnick, E., and Abramson, J.: Clinical Experiences with a New Orally Administered Mercurial Diuretic. New England J. Med. **249:** 681 (Oct. 22), 1953.

Fifteen ambulatory patients with severe congestive heart failure were treated with an oral mercurial diuretic, Neohydrin, for periods of 6 weeks to 18 months. The initial dose for most patients was three tablets every morning, and this amount was gradually increased until an effective level was reached. The diuretic was given in a single dose shortly after

breakfast for six days of each week. Additional treatment consisted of digitalis, low salt diets, and ammonium chloride. In 13 cases the results as measured by improvement of symptoms and physical signs were considered good. Only four patients had toxic manifestations, and no patient showed the clinical syndrome associated with excessive diuresis. In most cases Neohydrin replaced parenteral administration of mercurial diuretics. In several cases cardiac compensation was obtained with Neohydrin in patients who had been decompensated despite the use of cation exchange resins and frequent injections of mercurial diuretics. Nine patients in this group had been on another oral mercurial diuretic, (Salyrgan-theophylline Oral) previously. In most cases Neohydrin, although it contains less mercury than this preparation, was superior to Salyrgan-theophylline Oral in its diuretic action, both in the completeness of relief of congestion and in the maintenance of compensation.

SAGALL

James, W. E., Wisenbaugh, P., and Shumway, N.: Pain Caused by Potassium Intoxication in a Patient with Kimmelstiel-Wilson Syndrome. J.A.M.A. **153:** 545 (Oct. 10), 1953.

A case of unusual pain in a patient with Kimmelstiel-Wilson syndrome associated with potassium intoxication is reported. The patient intermittently complained of a cramping, knawing ache in his calves that spread to his upper extremities, hands and jaws as it became severer. A rise in the level of serum potassium and electrocardiographic T-wave changes consistent with hyperkalemia were observed during the interval of severe pain. This was controlled by administration of glucose and insulin and was easily reproduced by administration of excess potassium. The report illustrates the possible danger of treating a diabetic patient who has renal disease (for example, Kimmelstiel-Wilson syndrome) with fluids that are rich in potassium, such as orange juice and broth.

KITCHELL

PHYSICAL SIGNS

Bean, W. B., and Schmidt, M. C.: Rupture of the Aortic Valve. J.A.M.A. **153:** 214 (Sept. 19), 1953.

The aortic valve may rupture after some unusual stress or strain, or it may rupture when the valve is disorganized by bacterial endocarditis. Because of the notorious variability of murmurs the diagnosis is difficult where vegetations distort or dilate the valves. The authors report a case of rupture of the aortic valve diagnosed before death in the course of subacute bacterial endocarditis. They point out the abrupt decline and disappearance of the diastolic arterial blood pressure, the sudden pain, the advent or increase in congestive failure, and the appearance or change in aortic diastolic murmur as important diagnostic signs in the rupture of a diseased aortic valve.

KITCHELL

Björkman, S. E.: On the Occurrence of a Vascular Murmur over Greatly Enlarged Spleens. Acta med. scandinav. **145:** 79 (Fasc. 2), 1953.

The author describes a vascular murmur, synchronous with the pulse which has been found in 11 instances of splenomegaly. The murmur was recorded phonocardiographically in eight cases. The murmur is heard over greatly enlarged spleens with the lower pole reaching at least to the umbilical level. The murmur is very soft and of rather long duration. In phonocardiographic tracings the first and second heart sounds are also frequently registered, but these are believed to be transmitted from the heart. The murmur is believed to arise in the spleen rather than propagated from the heart because: (1) it may be heard over the spleen in patients who have no cardiac murmur at all, (2) if there is a cardiac murmur the splenic murmur is longer in duration and higher in pitch, (3) in one case there was a thrill over the spleen, synchronous with the murmur, and (4) phonographic records show the murmur beginning before the conducted first sound appears. It is postulated that the murmur results from the summation of numerous inaudible murmurs generated as the blood pours from narrowed afferent sheathed capillaries into greatly dilated splenic sinuses. It is felt that the appearance of a murmur may be related to the number of dilated sinuses in the enlarged spleen and as such may serve as a bedside evidence of hypersplenism.

ROSENBAUM

Magri, G.: Phonocardiography in Congenital Heart Disease. Minerva Med. **14:** (2), 1732, 1953.

The author studied 75 cases of congenital heart disease by means of the phonocardiograph. The diagnosis was confirmed by catheterization, angiocardiography, or surgery.

In *patent ductus arteriosus* (eight cases), the well-known continuous systolic-diastolic murmur was confirmed.

In *atrial septal defect* (six cases), a diamond-shaped pulmonic murmur was found in all; one of the cases also had a faint early-diastolic murmur; two other cases, either a presystolic or a diastolic rumble. The second sound was split in four cases.

In *ventricular septal defect* (eight cases), a diamond-shaped systolic murmur was recorded over the third left intercostal space; in two cases, a presystolic murmur was also recorded. The second sound was split in three cases. A third sound was present in all.

In *Eisenmenger complex* (three cases), a faint systolic pulmonic murmur, a loud pulmonic second sound, and a high-pitched, early-diastolic, pulmonic murmur, were recorded.

In *pulmonic stenosis* (five cases), a loud, diamond-

s aped pulmonic murmur and a faint second pul- n onic sound, were recorded. Similar data were ob- t ined at the right of the sternum in *aortic stenosis.*

Less typical data were found in the *trilogy* and *t ralogy of Fallot* and in *tricuspid atresia.*

These data are considered as obtained on a too li nited group of patients for having diagnostic i nportance. However, they represent an interesting c ntribution to the study of congenital heart d seases.

LUISADA

PHYSIOLOGY

Hajdu, S.: Mechanism of Staircase and Contracture in Ventricular Muscle. Am. J. Physiol. **174:** 371 (Sept.), 1953.

Hearts which have been stopped recover through a "staircase." The author considers this to mean that each contraction creates a more favorable environment for the next but that in time this degenerates. Loss of 127 mEq. of potassium per liter of fiber water characterizes this "favorable condition." This potassium re-enters during rest. The height of tension is determined by the equilibrium between these two processes since they determine the internal ion content. When 3 mEq. of potassium are lost from 106.8 mEq. of internal sodium and potassium, the tension is increased from 0 to 100 per cent. A similar effect on tension is produced by loss of internal sodium. Water lost with potassium does not change the internal ion concentration. When loss or gain in water occurs by itself and thus produces a change in internal ion concentration there is no effect on tension. Contractile protein is affected by total internal ion, not by concentration. Digitalis blocks by preventing re-entry of potassium. In this manner, the internal ion content is decreased. Excessive loss in internal ion causes contracture. Changes in membrane potential depending on external potassium influence the speed of appearance of contracture. Decreases in external potassium delay it and vice versa. The more internal ion content decreases the higher is the membrane potential required to prevent contracture. The resting potential promotes the dissociated contracted form of actomyosin in a situation where the associated or contracted form is favored. That the resting potential does this by maintaining a decreased intracellular pH is supported by the data at hand.

OPPENHEIMER

Swan, H., Zeavin, I., Holmes, J. H., and Montgomery, V.: Cessation of Circulation in General Hypothermia. I. Physiologic Changes and Their Control. Ann. Surg. **138:** 360 (Sept.), 1953.

The changes produced by general hypothermia were studied in three human subjects and in a series of dogs. In the case of the former group, the investigation was carried out while pulmonary valvulectomy was being done under direct vision, with cessation of blood flow for from three and one-half to seven and one-half minutes. In the case of the dogs, body temperature was dropped using ice water between 20 C. and 25 C.

With regard to alterations in blood chemistry, a fall in serum potassium was consistently noted during the period of hypothermia, while serum sodium levels remained constant. In the series of dogs ventricular fibrillation was found to occur either during cooling below 26 C., during cardiac manipulation, particularly ventricular incision, or immediately following restoration of circulation after occlusion. The administration of a potassium solution was believed to be useful in defibrillating the cold heart.

ABRAMSON

RHEUMATIC FEVER

McVay, L. V., and Sprunt, D. H.: Aureomycin in the Prophylaxis of Rheumatic Fever. New England J. Med. **249:** 387 (Sept. 3), 1953.

The report is concerned with the use of Aureomycin as a prophylactic agent in 35 rheumatic patients. Twenty-three patients were given Aureomycin containing the methyl and propyl esters of para-aminobenzoic acid (paraben), and the remaining 12 patients received a placebo as a control group. The average ages of the two groups were 17 years and 16 years respectively. The two groups of patients were comparable in all major respects. Doses of 250 mg. of Aureomycin were given 30 to 60 minutes before breakfast and again two hours after the evening meal. Five recurrences of rheumatic fever occurred in the course of this study in which the period of observation ranged from 2 to 20 months; four of them occurred in the control group and one occurred in the aureomycin series. Side affects of Aureomycin included nausea, vomiting, diarrhea, constipation, increased flatulence, pruritus ani and pruritus vulvae. It was necessary to discontinue the drug because of toxicity in only a single instance. The possible development of resistance by streptococci to Aureomycin was studied in this series and by the same authors in a group of 400 geriatric patients observed over a period of 15 to 21 months. The conclusion was that long-term administration of 500 mg. of Aureomycin daily does not result in the development of significant resistance by Group A beta-hemolytic streptococci. A reduction in respiratory infections of approximately 50 per cent was observed in the patients receiving Aureomycin. The conclusion of these observers is that Aureomycin is a promising prophylactic agent for rheumatic fever. The expense of this antibiotic is felt to represent its greatest disadvantage.

ROSENBAUM

Deane, N., Ziff, M., and Bunim, J. J.: Effects of Corticotropin on Body Water and Electrolytes in Patients with Rheumatic Disease. J. Clin. Invest. **32:** 879 (Sept.), 1953.

In order to quantitate some aspects of the changes in body water and electrolyte metabolism during induced adrenal cortical hyperfunction, four patients with rheumatic diseases were treated with corticotropin (ACTH) for periods ranging from 19 to 43 days. Two patients retained water intracellularly during the first week. Simultaneously, there was a shift of extracellular water into the cells. Further treatment restored the decrease in extracellular fluid volume. In two other patients there was a decrease in intracellular water during the period of therapy. Sodium retention was induced in three patients and was shown by a rise in total body sodium. Most, if not all, of this retained sodium was in the nonextracellular phase. In two of three patients there was retention of chloride chiefly as nonextracellular chloride. From this and other observations the authors conclude that under the conditions of this experiment markedly different patterns of response to corticotropin may be observed.

WAIFE

Kuschner, M., and Levieff, L.: Correlation between Active Rheumatic Lesions in the Left Auricular Appendage and Elsewhere in the Heart. Am. J. M. Sc. **226:** 290 (Sept.), 1953.

The authors examined 40 rheumatic hearts obtained at necropsy comparing the incidence of Aschoff bodies as an indication of rheumatic activity in the left auricular appendage with other areas of the myocardium. The auricular appendage contained Aschoff bodies in nine instances, with active lesions being described in other myocardial areas in each case. In six of the hearts, the left auricular appendage revealed no signs of activity while other areas revealed active lesions. Therefore, the absence of lesions within the left auricular appendage obtained during cardiac surgery does not preclude the possibility of activity elsewhere in the heart. However, the presence of rheumatic activity in the auricular appendage would seem to indicate that lesions are likely to be present at other sites in the heart.

SHUMAN

ROENTGENOLOGY

Dubilier, W., Burnett, H. W., Dotter, C. T., and Steinberg, I.: Radiation Hazard during Angiocardiography. Am. J. Roentgenol. **70:** 441 (Sept.), 1953.

The authors measured the amount of radiation received by patients and physicians in the course of angiocardiography. The patients received between 3.3 and 6.8 r (3300–6800 milliroentgens) with an average of 4.6 r. The physician injecting the radiopaque substance received 41 to 132 mr, an average of 78 mr when a large cone was used, and 31 to 101 mr, an average of 45 mr when a smaller cone was used. Scatter radiation was decreased two thirds by the use of a three-ply lead glass fabric (Archer lead glass gown).

The weekly permissible *total body dose* recommended by the National Committee on Radiation Protection is 300 mr, and the upper limit *on hands* as determined by the International Commission on Radiological protection is 1.5 r (1500 mr). The authors conclude that the amount of radiation during angiocardiography is safe when performed by standard methods.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Cronkhite, L. W.: Intracardiac Puncture in Cardiac Arrest. Multiple Episodes of Ventricular Asystole with Survival. New England J. Med. **249:** 8 (July 2), 1953.

The case of a woman aged 70 years who had repeated attacks of complete and prolonged ventricular standstill is described. The periods of ventricular asystole were preceded by evidence of marked ventricular irritability with ventricular tachycardia and ventricular fibrillation. In one 24 hour period there were 23 separate episodes of ventricular standstill, and on each occasion the heart was made to beat by the introduction of a cardiac needle into the ventricular wall. At no time was any medication introduced directly into the heart. Medication included quinidine, procaine amide hydrochloride, atropine sulfate and epinephrine. The attacks gradually subsided and the patient ultimately recovered. It is suggested that cardiac puncture is a quick and simple procedure which may be employed in cardiac standstill when more elaborate equipment for diagnosis and treatment of the condition is being assembled.

ROSENBAUM

Woodruff, W., and Merkel, C. G.: Decisions in Thoracic Surgery as Influenced by the Knowledge of Pulmonary Physiology. J. Thoracic Surg. **26:** 156 (Aug.), 1953.

On the basis of studies of patients subjected to thoracic operations, the authors present certain views which are practical and helpful guides in making surgical decisions in the presence of respiratory problems. They point out that the lungs and thorax act as the pump which brings air to the pulmonary capillary bed for gaseous exchange. In the normal individual the factor limiting peak physical exertion is not the respiratory, but the cardiovascular system. The capacity of the respiratory apparatus to pump air is dependent upon the integrity of the thoracic parietes, the existence of unimpeded airways, and the presence of norma

distensibility of the lungs. The pulmonary capillary bed has the ability to augment its capacity markedly through an increase of cross-section area of the capillaries and perhaps by an opening of previously nonperfused vessels.

The authors believe that pulmonary function studies are valuable in the over-all assessment of an individual prior to thoracic surgery, and are necessary in borderline cases.

ABRAMSON

Bailey, C. P., Bolton, H. E., Jamison, W. L., and Neptune, W. B.: Atrio-septo-pexy for Interatrial Septal Defects. J. Thoracic Surg. **26:** 184 (Aug.), 1953.

The authors reviewed the various procedures utilized in the surgical treatment of interatrial septal defects and presented another method consisting of atrioseptopexy. This involved bridging the defect with a portion of the invaginated right auricular wall. The operation was performed on 14 patients. Besides the septal defect, 2 had co-existing mitral stenosis, while 5 demonstrated anomalous entrance of the pulmonary veins either into the right atrium, the superior vena cava, or both. Twelve patients survived surgery while two died on the operating table. Three succumbed subsequently. Of the remaining nine, postoperative catheterization was carried out in six instances and of this number, four revealed complete abolition of the shunt and correction of the defect and associated lesions. In the other two, signs of a small residual interatrial communication were still found. The clinical improvement was considered to be excellent in all the surviving patients.

ABRAMSON

Julian, O. C., Grove, W. J., Dye, W. S., Olwin, J., and Sadove, M. S.: Direct Surgery of Arteriosclerosis: Resection of Abdominal Aorta with Homologous Aortic Graft Replacement. Ann. Surg. **138:** 387 (Sept.), 1953.

The authors reported the results of resection of the lower abdominal aorta, with replacement by an arterial bifurcation homograft, in five patients. Three of these suffered from arteriosclerotic obstruction of the bifurcation, while the remaining two had an aneurysm of the lower end of the abdominal aorta extending into both common iliac arteries. During the operation it was found advantageous to utilize medications to reduce blood pressure, so that trauma to the proximal portion of the aorta at the point of application of the clamp was minimized. Anticoagulants were not used.

Two of the grafts were successful in restoring pulsatile flow in both extremities, while in the other three this occurred on one side only. There were no deaths in the series.

ABRAMSON

Geoghegan, T., and Lam, C. R.: The Mechanism of Death from Intracardiac Air and Its Reversibility. Ann. Surg. **138:** 351 (Sept.), 1953.

The authors investigated the cause of death from air injected into the arterial tree in a series of dogs. None of the animals succumbed immediately after 0.25 to 2.0 cc. of air per kilogram of body weight was injected into the left carotid artery. However, there was evidence of marked neurologic damage when doses of more than 0.25 cc. were given. Another series of animals received 0.75 cc. of air per kilogram into the left ventricle, and only one survived. The large mortality was due to the entrance of air into the coronary arteries. However, the change was not irreversible, since many of the hearts were completely resuscitated by obtaining a high enough pressure in the coronary arteries to force the air through to the venous side. This was accomplished by clamping the aorta and applying manual systole.

ABRAMSON

Shumacker, Jr., H. B.: Surgical Repair of Atrial Septal Defects. Ann. Surg. **138:** 404 (Sept.), 1953.

The author described a new surgical approach to the closure of atrial septal defects. This involved fixing to an incision in the right atrium a pocket of autogenous pericardium which could be invaginated into the atrial cavity—one wall of which could be sutured directly to the margins of the defect. The operation was performed on two patients but the results were not satisfactory. In one, disintegration of the graft occurred, while in the other there was evidence suggestive of a persistent intra-arterial communication.

ABRAMSON

Deterling, Jr., R. A.: Resection of an Acquired Coarctation of the Low Thoracic Aorta and Replacement With a Preserved Vessel Graft. J. Thoracic Surg. **26:** 290 (Sept.), 1953.

The author presented the case of a 23 year old girl with a long coarctation of the lower portion of the thoracic aorta which was treated by excision and replacement by a preserved aortic homograft. Postoperatively a left hemothorax occurred, possibly due to a leak from an aortic fracture caused by the proximal aortic clamp. However, resolution of this process occurred and the end result was satisfactory. The blood flow in the lower extremities was normal after operation.

Because of the character and the site of the lesion, the author suggested that the patient may have had an acquired coarctation.

ABRAMSON

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7–9170

RESEARCH FELLOWSHIPS AND GRANTS
FOR THE FISCAL YEAR BEGINNING JULY 1, 1955

Fellowship Support

Applications must be received on or before September 15, 1954.

Research Fellowships (postdoctoral), open to graduates of approved medical or graduate schools, for research in the cardiovascular field. Awarded for periods of one or two years. Fellows must engage full-time in research. Stipend ranges from $3,500 to $5,500.

Established Investigatorships, open to graduates of approved medical or graduate schools who intend to follow an academic or investigative career. A Doctorate in Medicine, in Philosophy or in Science, and research achievement is required. Awarded for periods up to 5 years subject to annual review. Support offered in the field of cardiovascular or in fundamental research. Initial stipend is usually $6,000 with annual increases. Institutions may supplement stipend with permission of the Research Committee of the American Heart Association.

Research Grants-in-Aid

Applications must be received on or before December 1, 1954.

Grants are made to nonprofit institutions in direct support of a particular investigator, for a specific program of research under his direction. Grants are awarded in support of research in the cardiovascular field or basic sciences related to it in amounts up to $10,000 per annum for periods of one or more years.

Further information and application forms may be secured from the Medical Director.

SECOND WORLD CONGRESS OF CARDIOLOGY AND 27TH SCIENTIFIC SESSIONS OF AMERICAN HEART ASSOCIATION WASHINGTON, D. C., SEPT. 12–17

Schedule of Events

Saturday, Sept. 11, 5:00 to 10:00 p.m.: Registration, Mayflower Hotel

Sunday, Sept. 12:

9:00 a.m. to 10:00 p.m.: Registration, Mayflower Hotel

10:30 a.m.: Opening ceremonies at Constitution Hall

9:00 p.m.: Reception for Congress Members, Pan American Building

Monday, Sept. 13 through Friday, Sept. 17: Scientific Sessions at National Guard Armory. (See program below.)

Monday Sept. 13, 8:30 to 10:30 p.m.: Visit to National Gallery of Art, for Congress Members only.

Tuesday, Sept. 14, 8:00 p.m.: Formal banquet for Congress Members, to be held simultaneously at the Mayflower and Statler Hotels.

Wednesday, Sept. 15, 2:30 to 5:30 p.m.: Medical sightseeing tours.

Thursday, Sept. 16, 8:30 p.m.: Concert by the National Symphony Orchestra of Washington.

Friday, Sept. 17, 2:30 to 5:30 p.m.: Medical sightseeing tours.

Scientific Program

The scientific program of the Congress will be held at the National Guard Armory from Monday, September 13 through Friday, September 17. Morning sessions are scheduled daily from 9:00 to 12:30 p.m. Afternoon sessions will be held from 2:00 to 5:30 p.m. ever

day except Wednesday, Sept. 15 and Friday, Sept. 17 when medical tours are scheduled. Panels, symposia and special lectures will be held in the Main Auditorium. Simultaneous scientific sessions will be conducted in smaller rooms. The overall scientific program of the Congress is as follows:

MONDAY MORNING SEPTEMBER 13

Main Auditorium, Room A

SESSION I: 9:00–10:30 A.M.

International Cardiovascular Epidemiology

Paul D. White, Boston

Symposium: Atherosclerosis
Chairman: Ancel Keys, Minneapolis

Problems and Challenges of Population Comparisons. Ancel Keys, Minneapolis.
Wartime Lessons from Northern Europe on Arteriosclerotic Heart Disease. Gunnar Biorck, Malmö, Sweden.
Analysis of 10,000 Postmortem Examinations in Japan. Noboru Kimura, Kyushu, Japan.
Arteriosclerotic Heart Disease Among the Bantu of Johannesburg, South Africa. J. Higginson, Johannesburg.
Incidence of Coronary Disease in Population Groups in England. J. N. Morris, London.
Field Studies in Italy, 1954. Ancel Keys, Minneapolis.
Clinical Surveys in Italy. Paul D. White, Boston.
Discussion

INTERMISSION: 10:30–11:00 A.M.

SESSION II: 11:00–12:30 P.M.

Symposium: Other Cardiovascular Relationships
Chairman: Paul D. White, Boston

Rheumatic Fever. Vittorio Puddu, Rome.
Hypertension. Alberto C. Taquini, Buenos Aires.
Congenital Heart Disease. Pierre Soulie, Paris.
Cardiovascular Syphilis. J. Earle Moore, Baltimore.
Cor Pulmonale. Gordon S. Myers, Boston.
Endomyocardial Disease of Unknown Cause. J. N. C. Davies, Ampala, Uganda, South Africa.
Discussion

Simultaneous Scientific Sessions

ROOM B. Electrocardiography, I

Electrocardiographic Changes following Biliary and Gastric Distention in Freshly Infarcted Unanesthetized Dogs. Samuel Bellet, Richard L. Wechsler, Paul Nemir, Allan Kaplan and George Meade, Philadelphia.
Intermittent Patterns of Preponderance in Electrocardiographic Tracings. Marcel Segers, Brussels.
Bilateral Bundle Branch Block. Mauricio B. Rosenbaum, Buenos Aires.
The Electrocardiogram in Mitral Stenosis before and after Commissurotomy. J. Gilbert-Queralto, M. Torner-Soler and I. Balaguer-Vintro, Barcelona.
The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy in Rheumatic Heart Disease. Richard Turner, Edinburgh.
Considerations Regarding the Genesis of the QRS Complex in Pulmonary Embolism. Alberto H. Guardo, Enrique Lopez, Mahelz Molins and Francisco J. Romano, Buenos Aires.
Sino-Auricular-Ventricular Pathways. Roberto V. Lombardini, Eugenio J. Isasi, Roberto V. Garabelli and Antonio F. Mader, Montevideo, Uruguay.
Electrical Resistivity and Capacity of Living Body Tissues at Heart Signal Frequencies. Herman P. Schwan, Calvin F. Kay, Paul T. Bothwell and Elwood L. Foltz, Philadelphia.

ROOM C. Drugs and Therapy, I

Hypoproteinemia in Refractory Cardiac Edema. A. A. Fitzgerald Peel, Glasgow, Scotland.
Clinical Studies on Neriifolin. Jorge E. Bernal-Tirado and Julio C. Rico, Bogota, Colombia.
Long Term Anticoagulant Therapy. William T. Foley, Irving S. Wright, Ellen McDevitt and Cecil Simmons, New York.
Nicotinic Acid in the Treatment of Cardio-Respiratory Failure: Physiopathologic Bases and Clinical Experience. Luigi Condorelli and Pier Luigi Guidotti, Rome.
The Treatment of Incapacitated Euthyroid Cardiac Patients with Radioactive Iodine. Herrman L. Blumgart, A. Stone Freedberg and George S. Kurland, Boston.
The Action of Quinidine and Procainamide on the Excitability Conduction Rate and Refractory Period of Heart Tissue. Maria Isabel Rodriguez and Rafael Mendez, Mexico City.
Studies on Digitalis. Bernard Lown and Samuel A. Levine, Boston.
An Experimental Study of the Action of Sparteine on Auricular Flutter and Fibrillation. Rafael Mendez and Maria Isabel Rodriguez, Mexico City.

ROOM 12W. Physiology, I

The Metabolism of the Heart. Richard Bing, Birmingham, Alabama.
Results of Electronmicroscopic Investigations of Heart and Blood Cells. Bruno Kisch, New York.
Effect of Tissue Extracts on Oxygen Consumption by Homogenized Myocardial Tissue. Janet M.

Lemley-Stone and George R. Meneely, Nashville, Tennessee.

Molding of Blood Vessels, Valves and Stenotic Lesions by Hydraulic Forces. Simon Rodbard, Chicago.

The Influence of Rapid Infusion of Isotonic Glucose on the Pulmonary and Renal Circulation in Normal Individuals and in Cases with Mitral Stenosis. Lars Werko, Jan Ek, Harje Bucht and Edvardas Varnauskas, Stockholm.

The Effect of the Valsalva Maneuver on Net Pulmonary Artery Pressure. G. de J. Lee, M. B. Matthews and E. P. Sharpey-Schafer, London.

Hypothalamic Influences on Pulmonary Circulation. C. Bartorelli and G. Folli, Milan.

Experimental Unilateral Pulmonary Artery Occlusion in Humans. B. L. Brofman, Cleveland.

ROOM 27E. Occupational Cardiology and Rehabilitation

Occupational Outlook of Cardiacs: Experience of the Cleveland Work Classification Clinic. Herman K. Hellerstein, Elaine Goldstone, T. William Moir and Norman Harris, Cleveland.

Rehabilitation of the Patient with Cardiovascular Disease—the Third Phase of Medical Care. Joseph G. Benton and Howard A. Rusk, New York.

Cases Returning to Occupations following Myocardial Infarction. William D. Stroud, Morris W. Stroud III, and Joseph A. Wagner, Philadelphia.

Work Capacity of the "Disabled" Cardiac. Abraham Jezer, Bronx, New York.

Heart Disease and Industry, with Particular Reference to Workmen's Compensation Cases. Meyer Texon, New York.

An Experiment in Interprofessional Group Conferences for Cardiac Program Personnel. Ruth Whittemore, New Haven.

Mass Survey Technique in Heart Disease. A. Calhoun Witham and H. B. Jones, Augusta, Georgia.

Flying Stress and Heart Disease. Ashton Graybiel, Pensacola, Florida.

MONDAY AFTERNOON SEPTEMBER 13

Main Auditorium, Room A

SESSION III: 2:00–3:30 P.M.

Symposium: The Clinical Value of Instrumental Methods of Diagnosis in Congenital Heart Disease (to the Exclusion of X-ray and Electrocardiography)

Chairman: Andre Cournand, New York

The Relative and Absolute Value of These Methods in Congenital Lesions with Reduced Pulmonary Circulation. Maurice Campbell, London.

The Relative and Absolute Value of These Methods in Congenital Lesions with Increased Pulmonary Circulation. Pierre Soulie, Paris.

Use of Indicator Substances. Howard B. Burchell, Rochester, Minnesota.

Angiocinematography. F. Grosse-Brockhoff, Bonn.

Angiocardiography in Two Planes and with Multiple Frames. John Lind, Stockholm.

The Visual Demonstration of Congenital Malformations of the Heart by Means of the Trajectory and Position of the Catheter. Rodolfo Limon Lason, Mexico City.

INTERMISSION: 3:30–4:00 P.M.

SESSION IV: 4:00–5:30 P.M.

Panel: Congenital Heart Disease: Indications for and Results of Operations in Patent Ductus Arteriosus, Coarctation of the Aorta, Pure Pulmonic Stenosis and Tetralogy of Fallot

Chairman: Helen B. Taussig, Baltimore, Maryland
Co-Chairman: H. A. Snellen, Leiden, Netherlands
Assistant: Jorge Espino-Vela, Mexico City

Maurice Campbell, London
M. Durand, Paris
Stanley Gibson, Chicago
Rudolfo O. Kreutzer, Buenos Aires
Gustav Nylin, Stockholm

Simultaneous Scientific Sessions

ROOM B. Coronary Artery Disease

Immediate and Late Myocardial Changes in Experimental Infarction: Correlation of Oxygen Tension, Myocardial Dynamics and Local Electrocardiographic Data with Residual Scarring. W. F. Sheldon, J. J. Sayen, G. Peirce and P. T. Kuo, Philadelphia.

A Four Year Experience in the Treatment of Angina Pectoris by Internal Mammary Artery Implant, Supplemented by Pericardial Fat Grafts. Arthur Vineberg, D. D. Munroe, William Buller, and Yues Martineau, Montreal.

Infectious Coronaritis in the Pathogenesis of Myocardial Infarction. A. Turchetti and G. Lomeo, Rome.

Serum Glutamic-Oxalacetic Transaminase Activity in Myocardial Infarction. John S. LaDue, Felix Wroblewski and Arthur Karmen, New York.

The C-Reactive Protein Determination as a Measure of Myocardial Necrosis. Irving G. Kroop and Nathan H. Shackman, Brooklyn, New York.

Masculine Differentiation Index in Coronary Disease. J. Vague, A. Jouve, M. Teitelbaum, Marseilles.

Angina Pectoris in Women. T. Padilla, Buenos Aires.

The Work of the Heart at the Altitude of Bogota. Francisco Gnecco Mozo, Bogota, Colombia.

ROOM C. Drugs and Therapy, II

Paradoxical Effects from Nitroglycerine in the Treatment of Angina Pectoris. Henry I. Russek, Karl

F. Urbach and Burton L. Zohman, Staten Island, New York.

Comparison of the Hemodynamic Effects of Digitalis and of Mercurial Diuretics in the Treatment of Congestive Heart Failure. A. R. Berger, Bertha Rader and Warren W. Smith, New York.

Bioassay of Two Oral Mercurial Diuretics as Compared to Two Carbonic Anhydrase Inhibitors. John H. Moyer, Charles L. Spurr and Ralph V. Ford, Houston, Texas.

ACTH in Heart Disease: Its Paradoxical Effect on Sodium Excretion in Resistant Congestive Failure. F. R. Schemm and A. A. Camara, Great Falls, Montana.

Medical Management of Hypertension. Henry A. Schroeder and K. Mitchell Perry, Jr., St. Louis.

Long-Term Anticoagulant Therapy in Coronary Atherosclerosis. E. Sterling Nichol, Miami. (A Cooperative Study*)

An Evaluation of Continuous Long-Term Anticoagulant Therapy on the Prognosis of Myocardial Infarction. M. M. Suzman, H. D. Ruskin and B. Goldberg, Johannesburg.

Cardiovascular Disturbances and Their Treatment in Modified Electrotherapy for Psychiatric Illness. William Hall Lewis, Jr., D. Jeanne Richardson and Lawrence H. Gahagan, New York.

ROOM 12W. Physiology, II

Studies on Ventricular Filling. N. M. Buckley and Eric Ogden, Columbus, Ohio.

Oxygen Consumption of the Heart in the Heart-Lung Preparation. J. J. Van Heerswynghels, J. J. Reuse and M. J. Hans-Berteau, Brussels.

Circulatory Studies with Tagged Erythrocytes during Surgical Operations and Shock Conditions. Gustav Nylin, Stockholm.

Hepatic Rheography. J. Moniz de Bettencourt, Lisbon.

Interrelations of Arterial Oxygen Saturation and Coronary Circulation. Alfredo Alella, Rome.

Sodium and Cardiac Muscle. R. J. S. McDowall and A. F. Zayat, London.

Cardiocirculatory Studies in Pulsus Alternans of the Systemic and Pulmonary Circulations. M. Irene Ferrer, Rejane M. Harvey, Andre Cournand and Dickinson W. Richards, New York.

Venous Collateral Circulation after Ligation of Pulmonary Veins in the Dog. Massimo Calabresi, Alfred Hurwitz, Averill A. Liebow and Ronald W. Cooke, New Haven.

ROOM 27E. Mitral Stenosis

Electrocardiographic Changes during Mitral Commissurotomy. Harry Gross, Edith Kepes, Dennison Young and Charles D. Enselberg, New York.

The Results of Mitral Commissurotomy in 100 Cases with Preoperative Catheterization of the Heart. Ignacio Chavez, Manuel Vaquero and Felipe Mendoza, Mexico City.

The Influence of Pulmonary Vascular and Parenchymal Changes on the Success of Mitral Valvulotomy. B. C. Sinclair-Smith, J. F. Farrar, A. J. Palmer, J. H. Halliday and J. K. Maddox, Sydney, Australia.

Postoperative Hemodynamic Studies Carried out in 48 Cases of Mitral Stenosis. J. Carlotti, P. Soulié, F. Joly, J. R. Sicot and M. Degeorges, Paris.

The State of Lungs in Mitral Stenosis. J. Baillet, P. Chiche, M. Servelle and J. Carlotti, Paris.

A Technique for Pressure Measurements in the Left Atrium, Left Ventricle and Aorta. Viking Olov Bjork, Stockholm.

Some Aspects of the Surgical Treatment of Mitral Stenosis. Clemente Robles, Jenaro Pliego, Felipe Mendoza, Patricio Benavides, Fernando Quijano, Ruben Fernandez Pellon and Jose Roberto Monroy, Mexico City.

Prognosis of Mitral Stenosis. R. Vedoya, C. T. Nessi and J. Mendelzon, Buenos Aires.

TUESDAY MORNING SEPTEMBER 14

Main Auditorium, Room A

SESSION I: 9:00–11:00 A.M.

Rheumatic Fever

Chairman: J. G. Fred Hiss, Syracuse, New York

Experimental Studies on the Nature and Origin of Fibrinoid
Lewis Thomas, Minneapolis

Panel: Diagnosis and Management of Rheumatic Fever and Rheumatic Heart Disease

Chairman: T. Duckett Jones, New York

Edward F. Bland, Boston
Charles H. Rammelkamp, Cleveland
John D. Keith, Toronto
David D. Rutstein, Boston

INTERMISSION: 11:00–11:30 A.M.

SESSION II: 11:30–12:30 P.M.

George Brown Memorial Lecture

The Control of the Peripheral Circulation by the Walls of the Blood Vessels. Alan C. Burton, London, Ontario.

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* John J. Boehrer, Minneapolis; Joseph F. Borg, St. Paul, Minnesota; Thomas J. Coogan, Chicago; George C. Griffith, Los Angeles; John W. Keyes, Detroit; Edward Massie, St. Louis; William L. Mullins, Pittsburgh; Robert Page, Chicago; Thornton Scott, Lexington, Kentucky; Lawrence M. Serra, Baltimore; Charles A. L. Stephens, Tucson, Arizona.

Simultaneous Scientific Sessions

ROOM B. Pulmonary Heart Disease

Primary Pulmonary Hypertension. Lewis Dexter, Florence W. Haynes, Hiroshi Kuida, Murray Rabinowitz and Elliot Rapaport, Boston.

A Study of Seven Cases of Essential Pulmonary Hypertension. P. Soulie, R. Tricot, J. Dimatteo and J. Baillet, Paris.

Clinical and Microscopic Data on the Pulmonary Arterial Circulation of Either Venous or Arterial Overfilling of the Lungs (Mitral Stenosis; Patent Ductus Arteriosus or Septal Defects). H. A. Snellen, J. Dankmeyer and J. Ho-A-Sjoe, Leiden, Netherlands.

Compression of the Left Coronary Artery during Cor Pulmonale. Eliot Corday, Beverly Hills, California.

A Study of the Factors Causing Pulmonary Hypertension in Patients with Pulmonary Tuberculosis. A. Van Loo, R. Pannier, K. Vuylsteek, J. Verstraeten, A. Gyselen, R. De Brabandere, R. Verbeke, and M. Vanderstraeten, Lemberge, Belgium.

Effects of Priscoline on the Pulmonary Vascular Resistance and Arterial Blood Oxygen Saturation in Patients with Chronic Pulmonary Disease. David T. Dresdale, Alfred M. Steinman, Hyman Gold, Hernando Castellon and Jerome J. Greenwald, New York.

Hemodynamic Effects of Induced Systemic Hypotension upon Pulmonary Hypertension of Various Origins. Charles Lepine, Benito Carasso and Fernand Gregoire, Montreal.

Bilharzial Cor Pulmonale. M. Ibrahim and B. Girgis, Cairo.

ROOM C. Cardiovascular Surgery, I

The Course of Pulmonary Hypertension after Surgical Treatment of Mitral Stenosis: Evidence for Progressive Long-Term Improvement. J. Gerard Mudd, William F. Kistner and C. Rollins Hanlon, St. Louis.

Clinical Results of 500 Patients with Mitral Stenosis Undergoing Valvuloplasty. Lawrence B. Ellis and Dwight E. Harken, Boston.

The Immediate and Remote Results in 150 Cases of Mitral Valvulotomy. J. K. Maddox, J. H. Halliday, F. Mills, J. F. Farrar, A. J. Palmer and B. C. Sinclair-Smith, Sydney, Australia.

Surgical Treatment of Interatrial Septal Defects. Robert E. Gross, Boston.

Clinical Evaluation of the First 42 Patients with Severe Aortic Insufficiency, Treated with a Plastic Aortic Valve. C. A. Hufnagel, W. P. Harvey, J. P. Segal, R. Ari and P. Rabil, Washington, D. C.

The Results of Direct Operations on Pulmonary Stenosis in Fallot's Tetralogy. R. C. Brock, London.

Surgical Management of Pulmonary Valvular Stenosis: A Clinical and Physiological Postoperative Evaluation. C. Walton Lillihei, Paul Winchell, Paul Adams, Ivan Baronofsky, Forrest Adams and Richard L. Varco, Minneapolis.

Left Heart Surgery in Dogs during Respiratory and Cardiac Arrest at Body Temperatures below 10 Degrees Centigrade. James T. Grace, D. S. Tysinger, Merrill W. Schell and Frank Gollan, Nashville, Tennessee.

ROOM 12W. Electrocardiography, II

The Influence of Cortisone and Various Compounds on the T Wave of the Dog Electrocardiogram. Melville Magida and Rose Lubschez, New York.

Quantitative Exploration of the Electrical Field of the Heart. Pierre Rijlant, Brussels.

The Electrocardiographic Significance of Dipole Potentials Produced in Homogeneous Torso Models. Ernest Frank and Calvin F. Kay, Philadelphia.

The Pre- and Postoperative Electrocardiogram in Mitral Stenosis. D. Dimatteo, F. Joly, M. Degeorges and J. Carlotti, Paris.

The Mechanism of the Preventive Action of Induced Hypothyroidism on Experimental Ventricular Arrhythmias of the Rat. Fernando F. Batlle, Manuel Rene Malinow and Bernardo Malamud, Buenos Aires.

Ventricular Activation in Ventricular Extrasystoles. Alfonso Anselmi, Maria Isabel Rodriguez, and Demetrio Sodi-Pallares, Mexico City.

The Pharmacology of Experimental Ventricular Arrhythmias in the Rat. III. Effects of Quinidine, Quinine, Procaine, and Procaine Amide. Blas Moia, Manuel Rene Malinow, Fernando Batlle and Bernardo Malamud, Buenos Aires.

Wolff-Parkinson-White Syndrome in Ebstein's Disease: Possibility of Diagnosing Anomaly by Means of Intracavitary Leads. Demetrio Sodi-Pallares, Jorge Soberon Acevedo, Fernando Cisneros, Federico Marsico and Agustin Alvarado, Mexico City.

ROOM 27E. Arteriosclerosis and Cerebrovascular Disease

Experimental Atherosclerosis. S. B. Andrus, G. V. Mann and F. J. Stare, Boston.

The Interrelationship of Diet and Hormones in Atherogenesis. Ruth Pick, Jeremiah Stamler and Louis N. Katz, Chicago.

A Cholesterol Tolerance Test: Its Probable Usefulness in the Diagnosis of Coronary Atheromatosis. Roberto Francisco, San Juan, Puerto Rico.

The Genetics of Hypercholesterolemic Xanthomatosis. Edwin O. Wheeler, Boston.

Neurocirculatory Asthenia and Subclinical Arachnoiditis Adhesiva Cerebrospinalis. Magojiro Maekawa, Kyoto, Japan.

Cheyne-Stokes Breathing and Its Relation to Heart

Disease. James Hawley Currens, Rhett Talbert and Mandel E. Cohen, Boston.

Changes Produced by Heparin in Electrophoretic Lipid Pattern in Human Atherosclerosis. J. Gilbert-Queralto, I. Balaguer-Vintro and L. Grau-Codina, Barcelona.

Ultracentrifugal and Electrophoretic Studies of the Influence of Gonadal Steroids on Human Serum Lipoproteins in Relation to Atherosclerosis. Robert H. Furman, R. Palmer Howard, and Loyal L. Conrad, Oklahoma City.

TUESDAY AFTERNOON SEPTEMBER 14

Main Auditorium, Room A

SESSION III: 2:00–3:30 P.M.

Symposium: The Problems of Circulation
Chairman: George E. Burch, New Orleans
Co-Chairman: Grace M. Roth, Rochester, Minnesota

The Present Status of the Diagnosis of Pheochromocytoma by Pharmacologic Methods. Grace M. Roth and Walter F. Kvale, Rochester, Minnesota.

Diagnosis and Therapy for the Segmental Occlusion of the Major Arterial Supply. Gerald H. Pratt, New York.

Non-Cardiac Circulatory Congestion Simulating Congestive Heart Failure. Ludwig W. Eichna, Saul J. Farber, Adolph R. Berger and Bertha Rader, New York.

Factors which Determine the Rate of Venous Return to the Heart. Arthur C. Guyton, University, Mississippi.

3:30–3:45 P.M.

Paul White Prize Lecture of the Argentine Society of Cardiology

Methods for the Experimental Production of Generalized Atherosclerosis in the Rat. Manuel Rene Malinow, D. Johman and A. A. Pelligrino, Buenos Aires.

INTERMISSION: 3:45–4:00 P.M.

SESSION IV: 4:00–5:30 P.M.

Panel: The Treatment of Hypertension
Chairman: Eduardo Braun-Menendez, Buenos Aires
Co-Chairman: Irvine H. Page, Cleveland

Edgar V. Allen, Rochester, Minnesota
Stina Bjoerk, Uppsala, Sweden
George A. Perera, New York
Kenneth Shirley-Smith, London
F. Horace Smirk, Dunedin, New Zealand
Robert W. Wilkins, Boston

Simultaneous Scientific Sessions

ROOM B. Rheumatic Fever and Rheumatic Heart Disease, I

Histogenesis of Rheumatic Lesions. I. Costero, R. Barroso-Moguel and A. Chevez, Mexico City.

Electrocardiographic Studies in Active Rheumatic Fever. Luiz V. Decourt and Mateus Romeiro Neto, Sao Paulo, Brazil.

A Post-Mortem Study of the Left Atrial Appendage in 14 Cases of Acute Rheumatic Fever with Special Reference to Aschoff Bodies. A. Castellanos, Jr., J. M. Calvino and F. Sala Panisello, Havana.

Rationale and Results of Hormone Therapy in Rheumatic Fever. Vincent C. Kelley, Robert S. Ely and Alan K. Done, Salt Lake City.

A Histopathological and Clinical Study of Cardiac Lesions in Patients Subjected to Mitral Commissurotomy; the Effect of Cortisone on Such Lesions. Javier Robles Gil, Hector Rodriguez and Juan Jose Ibarra, Mexico City.

Use of Combined Therapy and Rebound Suppression in the Treatment of Rheumatic Fever. Edward E. Fischel and Charles W. Frank, Bronx, New York.

The Treatment of Cerebral Embolism from Mitral Stenosis. H. A. Dewar and S. G. Owen, Newcastle on Tyne, England.

Follow-Up Studies in Rheumatic Fever Patients—A Program of Social Cardiology. Gunnar Biorck, Malmö, Sweden.

ROOM C. Cardiovascular Surgery, II

The Surgical Treatment of Mitral Insufficiency. Charles P. Bailey, William L. Jamison and Henry T. Nichols, Philadelphia.

The Results of Valvulotomy in Pulmonary Stenosis with a Closed Ventricular Septum. Maurice Campbell, London.

Surgical Treatment of Coarctation of the Aorta Among the Newborn. J. Mathey, J. Nouaille, O. Schweistuth, J. P. Binet and J. Labesse, Paris.

Circulatory Dynamics 5 Years After Surgical Correction of Coarctation of the Aorta. J. Leo Wright, O. Theron Clagett, Howard B. Burchell, Edgar A. Hines, Jr., and Earl H. Wood, Rochester, Minnesota.

Anomalous Pulmonary Venous Drainage. Alexander S. Nadas, Walter T. Goodale and Robert E. Gross, Boston.

Treatment of Pulmonary Valvular Stenosis and of Tricuspid Stenosis with an Original Technique, Using a Modified Catheter. Victor Rubio and Rodolfo Limon Lason, Mexico City.

Inferior Vena Cava Ligation in Heart Failure: Experience of 5 Years in One Hundred Cases. J. Bernath, R. Guillemot, P. Samuel and R. Heim de Balsac, Paris.

An Analysis of Thromboembolic Data in 500 Cases of Mitral Stenosis: Preoperative State, Opera-

tive Findings, and Present Status. Robert P. Glover, Thomas E. O'Neill, O. Henry Janton and Bartholomeo Iaia, Philadelphia.

ROOM 12W. Electrocardiography, III

Ventricular Activation in the Dog's Heart. Demetrio Sodi-Pallares and Fernando Cisneros, Mexico City.

Experiences with Rudimentary Anterior Wall Infarction. Max Holzmann, Zurich.

The Distinctive and Mutable Electrocardiogram of Coronary Arteriospasm. William Evans, London.

The Myocardial Lesion in Constrictive Pericarditis: Electrocardiographic and Pathologic Observations. Harold D. Levine and George A. McLemore, Boston.

Thoracic Bipolar Horizontal Leads. Pedro Cossi and Alberto Bibiloni, Buenos Aires.

Clinical Study of the Abnormalities of the End-Complex TU-U of the Electrocardiogram. Joseph Lambert, Spa, Belgium.

Comparison of the T Waves of Hyperpotassemia with Similar T Waves in Other Conditions. Harold A. Braun, Borys Surawicz and Samuel Bellet; Philadelphia.

Experimental A.-V. Nodal Rhythm. F. Jourdan, R. Froment and C. Finas, Lyon, France.

ROOM 27E. Ballistocardiography

Displacement, Velocity and Acceleration Ballistocardiograms as Registered with an Undamped Bed of Ultra-Low Natural Frequency. Maurice B. Rappaport, Cambridge, Mass.

The Ballistocardiogram in Relation to Functional Capacity in a Group of Patients Affected by Different Heart Diseases. L. de Soldati, R. H. Mejia, C. M. Castro, G. Stritzler and M. Avellaneda, Buenos Aires.

Serum Cholesterol Concentration and Ballistocardiographic Characteristics of Middle-Aged Men. Henry L. Taylor and Joseph T. Anderson, Minneapolis.

The Effect of Alimentary Lipemia on Angina Pectoris and Circulatory Dynamics of Patients with Coronary Artery Disease. Peter T. Kuo and Claude R. Joyner, Jr., Philadelphia.

Further Long-Term Studies with the Ballistocardiogram, with a Note on the Changes in the Records of Certain Elderly Persons Induced by Nitroglycerine. Isaac Starr and Elaine Pedersen, Philadelphia.

Characteristics of the Ballistocardiogram in Persistent Patency of the Ductus Arteriosus. Augusto Mispireta, Angelica Corvacho, M. Escudero and Luis Goyzueta, Lima, Peru.

Ballistocardiography in Normal Pregnancy. Nogueira Dacosta and J. Moniz de Bettencourt, Lisbon.

The Ballistocardiogram and the Electrokymogram in Heart Block. J. Enderle, W. Cassiman, J. Van Heerswynghels and M. Segers, Brussels.

WEDNESDAY MORNING SEPTEMBER 15

Main Auditorium, Room A

SESSION I: 9:00–10:30 A.M.

Symposium: Blood Volume
Chairman: Gustav Nylin, Stockholm
Co-Chairman: Carl J. Wiggers, Cleveland

Physiological Aspects on the Regulation of Blood Volume. Hampden C. Lawson, Louisville, Ky.

The Use of Different Dye Methods in Blood Volume Determinations. Ernst Wollheim, Würzburg, Germany.

Comparison Between Different Radioactive Labelling Techniques of Red Cell Volume. Seymour J. Gray, Boston.

Residual Volume of Blood in the Right and Left Ventricles. Robert R. Rushmer, Seattle.

Physiological and Clinical Application of the Isotope Technique in Blood Volume Determination. P. Waser, Basel.

INTERMISSION: 10:30–11:00 A.M.

SESSION II: 11:00–12:30 P.M.

Symposium: The Physiology of the Contractile Protein in Heart Muscle
Chairman: Maurice B. Visscher, Minneapolis

Fundamental Aspects of the Chemistry and Behavior of Contractile Proteins. W. F. H. M. Mommaerts, Cleveland.

The Significance of the Newer Knowledge of Contractile Proteins to Cardiology. Richard J. Bing, Birmingham, Alabama.

Simultaneous Scientific Sessions

ROOM B. Rheumatic Fever and Rheumatic Heart Disease, II

The Role of the Mast Cell in the Reaction to Injury. Earl P. Benditt, Chicago.

An Improved Spectrophotometric Method for Determining Antistreptolysin-O. Harry A. Feldman and Anne L. Gillen, Syracuse, New York.

Cardiac Lesions Induced by a Proteolytic Enzyme Isolated from Filtrates of Group A Streptococci. Aaron Kellner and Theodore Robertson, New York.

The Relationship of the Immune Response to Group A Streptococci to the Course of Acute, Chronic and Recurrent Rheumatic Fever: A Study of 500 Patients. Gene H. Stollerman, Arthur J. Lewis, Irwin Schultz and Angelo Taranta, New York.

Clinical Course of Subcutaneous Nodules in Rheumatic Fever, and Its Significance in Relation to Treatment with ACTH and Cortisone. Benedict F. Massell and Alexander J. McDonald, Boston.

Functional Evaluation of Rheumatic Heart Disease and Mitral Valve Surgery by Standardized Exercise Tolerance Tests. Robert A. Bruce, James J. Pampush and K. Alvin Merendino, Seattle.

Recurrence of Rheumatic Fever Due to Commissurotomy. Y. Bouvrain, P. Fortin and M. Caramanian, Paris.

Current Concepts of the Management of Heart Disease in Pregnancy. Curtis L. Mendelson, New York.

ROOM C. Cardiopulmonary Dynamics

Atrial Septal Defect: Relationship of Interatrial Pressure Gradient to Right and Left Ventricular Work, with Effects of Surgical Closure. Walter T. Goodale, Roger B. Hickler and Alexander S. Nadas, Boston.

The Practical Application of the Compression Chamber Theory in Cardiac Catheterization. R. Knebel, Munster, Germany.

Elevated Right Ventricular Pressure and Its Relation to the Pattern of Right Ventricular Hypertrophy. M. Torner-Soler, I. Balaguer-Vintro and J. Gibert-Queralto, Barcelona.

Method for the Determination of Potency and Work of the Right Ventricle in Pulmonary Stenosis. H. J. Bidoggia, I. F. Cordero, F. E. Labaurt and E. R. Pietrofesa, Buenos Aires, Argentina.

Oxygen Content of Pulmonary Artery Blood During the Respiratory and Cardiac Cycle in Patients with Intracardiac and Great Vessel Shunts in Relation to Possible Errors in Measurement of Pulmonary Flow. John T. Shepherd, Earl H. Wood and Howard B. Burchell, Rochester, Minnesota.

Relations Between the Shape of the P. C. V. Pressure Pulse and the Physiopathology of the Mitral Valve. E. Coelho, S. Borges, F. Padua, M. I. Barata, J. Maltez, S. Pereira and C. A. Duarte, Lisbon.

Intracardiac Pressure Recordings in Arrhythmic Heart Action. E. Boden, Dusseldorf.

The Effects of Aortic Valvular Disease on Left Ventricular Function. Richard Gorlin, Michael B. Matthews, Raymond Daley, Ian K. R. McMillan and W. E. Medd, Jr., Boston.

ROOM 12W. Vectorcardiography

Comparative Value of Electrocardiographic and Vectorcardiographic Diagnosis: Pathological Correlation. A. M. Soffe, J. L. Richman and L. Wolff, Boston.

The Truth About Vectorcardiography. Franklin D. Johnston and Richard McFee, Ann Arbor.

An Electronic Analogue Computer for the Automatic Determination of the Ventricular Gradient in Man. Stanley A. Briller, Nathan Marchand and Charles E. Kossmann, New York.

The Electrical Artificial Heart. J. B. Milovanovich and A. J. Milovanovich, Paris.

A Study of the Electric Field of an Isolated Mammalian Heart in a Homogeneous Volume Conductor. Ines Hartmann, Robert Veyrat, Oscar A. M. Wyss and Pierre W. Duchosal, Geneva.

Wolff-Parkinson-White Syndrome: Clinical, Experimental, Electrocardiographic and Vectorcardiographic Studies. Ramon Aixala, Antonio Gomez, Raul Lopez, Pedro Fojo, Gabriel A. Sanchez, Julio Muniz, Rene Triay and Rene Sanchez, Havana.

Vectorial Representation of Bundle Branch Block Patterns from Scalar Leads. P. Rochu, P. Nicolai and A. Jouve, Marseilles.

A Study of the Spatial Vectorcardiogram and the Electrocardiogram in 117 Patients with Congenital Heart Disease. E. Donoso, E. Braunwald, S. Sapin, S. Blumenthal and A. Grishman, New York.

ROOM 27E. Congenital Heart Disease, I

Renal Function in Coarctation of the Aorta. C. Frederick Kittle, William L. Valk and Andrew D. Mitchell, Kansas City, Kansas.

At Which Stages of Human Development can the Origin of Congenital Heart Malformations be Located? J. Dankmeijer, Leiden, Netherlands.

The Genesis of Cyanosis in Eisenmenger's Complex. A. Agostini and G. Voci, Milan.

Pulmonary Tuberculosis Complicating Congenital Heart Disease with Reduced Pulmonary Blood Flow. S. D. Doff, Jacksonville, Florida.

Studies on the Circulation in Isolated Auricular and Ventricular Septal Defects. J. Lequime, H. Denolin, P. Courtoy and J. Kenis, Brussels.

Condorelli's Test for the Diagnosis of Ventricular Septal Defect. A. Turchetti, Rome.

Atypical Cases of Pulmonic Stenosis. P. Vernant, J. Nouaille, F. Bouchard and A. Piton, J. Mathey, Paris.

Report of Two Rare Cases of Transposition of the Great Blood Vessels. F. Grosse-Brockhoff and A. Schaede, Bonn.

THURSDAY MORNING SEPTEMBER 16

Main Auditorium, Room A

SESSION I: 9:00–10:30 A.M.

Panel: Surgery of Congenital Heart Disease
Chairman: Alfred Blalock, Baltimore
Co-Chairman: Russell Brock, London

Jean Mathey, Paris
Robert Gross, Boston
Clemente Robles, Mexico City
J. F. Nuboer, Utrecht, Netherlands
C. Walton Lillihei, Minneapolis

INTERMISSION: 10:30–11:00 A.M.

SESSION II: 11:00–12:30 P.M.

Panel: Surgery of Non-Congenital Heart Disease
Chairman: Robert Gross, Boston
Co-Chairman: Samuel A. Levine, Boston

R. Heim de Balsac, Paris
Robert P. Glover, Philadelphia
Charles A. Hufnagel, Washington, D. C.
John C. Jones, Los Angeles
J. Kenneth Maddox, Sydney, Australia

Simultaneous Scientific Sessions

ROOM B. Peripheral Vascular Disease

Surgical Modification of the Ischemic Index. E. A. Otero and Manuel Rene Malinow, Buenos Aires

Observations on a Soluble Long-Acting 4-Hydroxycoumarin. Shepard Shapiro, New York.

Experimental and Clinical Experience with Marcumar—A New Anticoagulant. René Bourgain, Cecil Symons and Irving S. Wright, New York.

Muscular Lesions of the Limbs in Arteritic Patients: Biopsy and Biochemical Findings. R. Scalabrino and P. G. Bianchi, Milan.

Clinical Investigation of the Oscillogram of Peripheral Arteries. M. G. Kettner, C. L. Ferrero and P. W. Duchosal, Geneva.

Responses of the Muscle Vessels to Temporary Arterial Occlusion in Normal and in Collateral Circulation. Joseph Lambert, Spa, Belgium.

Evaluation of Arteriography in the Study of Chronic Arterial Occlusions of the Lower Extremities. E. Perez-Stable, B. Milanes, R. Bustamante, A. Hernandez and J. MaCoock, Havana.

Treatment with Digitalis for the Ischemic Muscle in Chronic Arterial Insufficiency. Luis Mendez, Mexico City.

ROOM C. Hypertension, I

Severe Cardiovascular Disease and Hypertension Induced in the Albino Rat with the Help of Obstructive Nephropathy. David Lehr, Jacob Churg, Constance Martin and Robert Milora, New York.

An Evaluation of the Hypotensive Action of Rauwolfia Serpentina Alkaloids in Cases of Essential Hypertension. Rustom Jal Vakil, Bombay.

Rauwolfia Serpentina—Clinical and Metabolic Studies in Hypertensive Patients. George A. Perera, New York.

Some Observations on Water and Electrolyte Metabolism in Hypertension. A. C. Taquini, S. A. Plesch, T. A. Capris and B. N. Badano, Buenos Aires.

The Effect of Weight Reduction upon the Blood Pressure of Obese Hypertensive Patients. A. P. Fletcher, London.

Oral Protoveratrine in the Treatment of Hypertension. Mariano M. Alimurung and Maria Z. Grajo, Manila.

The Treatment of Hypertension with Hexamethonium and Hydergine. Francisco Rojas Villegas, Carlos Silva, Pablo Toledo, Alfredo Silva, Graciela Vera and David Brailovsky, Santiago.

Intractable Heart Failure—The Influence of Hypertension. John B. Johnson, Alphonzo Jordan, Clarence S. Greene and William Pogue, Washington, D. C.

ROOM 12W. Heart Diseases of Uncommon Etiology, I

Carcinoid of the Small Intestine and Right Heart Valvular Disease. Ake Thorson, Gunnar Biorck, Gunnar Bjorkman and Jan Waldenstrom, Malmö, Sweden.

Chagas' Cardiopathy: Clinical and Laboratory Considerations. Hugo Abitbol, Aldo Romero, Alfredo Lopez Martin (Mendoza), Ignacio Maldonado Allende, Ricardo B. Podio, Felipe Gonzales Alvarez, and P. B. Camponovo (Cordoba), Buenos Aires.

Right Bundle Branch Block in Chronic Chagasic Myocarditis. Mauricio B. Rosenbaum and Atdemar J. Alvarez, Buenos Aires.

The Diagnosis of Papiraceus Auricle. J. M. Rivero Carvallo and M. H. Ramirez Jaime, Mexico City.

A Re-evaluation of the Diagnostic Criteria for Acute Pericarditis. William A. Sodeman and Richard H. Smith, Columbia, Missouri.

Idiopathic Recurrent Pericarditis: A Comparison with the Postcommissurotomy Syndrome and Consideration of Etiology and Treatment. William Dressler, New York.

Chronic Constrictive Pericarditis—Its Detection in Apparently Healthy People. F. A. L. Mathewson, Winnipeg, Canada.

The Risks of Flying in Patients with Cardiovascular Disease: A Report on 30 Cases. Geoffrey Bourne, London.

ROOM 27E. Diagnostic Methods

The Jugular Pulse in Defects of the Interventricular Septum: Congenital and Acquired. David Gelfand, Philadelphia.

Left Auricular Pulsations in Mitral Valve Disease. Vittorio Puddu, Rome.

Measurement of Left Auricular Pressure (L.A.P.) by Transbronchial Route in Patients Suffering from Mitral Lesions. J. Facquet, P. Alhomme, J. M. Lemoine and J. J. Welti, Paris.

Transbronchial Puncture of the Left Atrium: Technique and Application of the Method in the Study of Congenital and Acquired Heart Disease. Andrew G. Morrow and William R. Milnor, Bethesda, Maryland.

The Valsalva Test in Mitral Stenosis. A. de Carvalho Azevedo, A. Alves de Carvalho, A. Ney Toledo and Robison Roubach, Rio de Janeiro.

Diagnosis of Tricuspid Insufficiency: Clinical Features in Sixty Cases with Associated Mitral Valve Disease. Gonzalo Sepulveda and Daniel S. Lukas, New York.

Electrophoretic Studies in Inflammatory Cardiovascular Processes. E. Donzelot, H. Kaufmann and G. Dauzier, Paris.

Correlation of Serial Cardiac Roentgenokymographic Patterns with the Clinical State in Myocardial Infarction. J. J. Sampson, B. Solomon, A. A. Goetz, Leland L. Felton and S. J. Axelrad, San Francisco.

ROOM F. Symposium: Vectorcardiography

9:00 A.M.–12:30 P.M.

Chairman: Pierre W. Duchosal, Geneva, Switzerland

Physical Foundation of Vectorcardiography. H. C. Burger, Utrecht, Netherlands.

The Normal Vectorcardiogram and the Classification of Abnormalities. W. R. Milnor and C. A. Bertrand, Baltimore.

Clinical Practice of Vectorcardiography. Andre Jouve, Marseilles.

The Spatial Vectorcardiogram in Left Ventricular Hypertrophy. L. G. Horan, George E. Burch, J. A. Abildskov and J. A. Cronvich, New Orleans.

THURSDAY AFTERNOON SEPTEMBER 16

Main Auditorium, Room A

2:00–2:15 P.M.

Memorial to Dr. Frank N. Wilson. Louis N. Katz, Chicago.

2:15–2:30 P.M.

Memorial to Dr. Willem Einthoven. H. A. Snellen, Leiden, Netherlands

SESSION III: 2:30–4:00 P.M.

Panel: Electrocardiography
Chairman: Louis N. Katz, Chicago
Co-Chairmen: Charles E. Kossmann, New York, George E. Burch, New Orleans

The Standard Electrocardiogram:

Max Holzmann, Zurich
Gordon B. Myers, Detroit
Vittorio Puddu, Rome
Marcel Segers, Brussels
Demetrio Sodi-Pallares, Mexico City
Ginger Williams, Boston

The Stereovectorcardiogram:

W. Den Boer, Utrecht, Netherlands
Pierre W. Duchosal, Geneva
Arthur Grishman, New York
Andre Jouve, Marseilles
J. B. Milovanovich, Paris
Louis Wolff, Boston

INTERMISSION: 4:00–4:15 P.M.

SESSION IV: 4:15–5:30 P.M.

Panel: Ballistocardiography
Chairman: Isaac Starr, Philadelphia

Benjamin Baker, Baltimore
Herbert R. Brown, Jr., Rochester, New York
Tinsley R. Harrison, Birmingham, Alabama
Harry Mandelbaum, Brooklyn, New York
John L. Nickerson, New York

Simultaneous Scientific Sessions

ROOM B. Hypertension, II

Hemodynamics of Acute Hypertension Produced by Stimulation of Cerebral Cortex. H. G. Langford, J. L. Patterson, Jr., R. R. Porter, M. Bernhaut and E. C. Hoff, Richmond, Virginia.

The Neurogenic Component in Hypertension. F. Horace Smirk and Austin E. Doyle, Dunedin, New Zealand.

The Thyroid in Experimental Renal Hypertension. Eduardo Braun-Menendez, Buenos Aires, Argentina.

The Effects of a Low Sodium Diet on the Chemical Composition of the Arterial Wall in Normal Rats and in Rats with Renal and Desoxycorticosterone Hypertension. Louis Tobian, Jr., Dallas.

Pharmacodynamics of Hypotensive Drugs. Benedict E. Abreu, Alice B. Richards and Carl A. Bunde, Indianapolis.

The Use of Hexamethonium Bromide in the Prevention and Treatment of Left Ventricular Failure. K. Shirley Smith and P. B. S. Fowler, London.

The Treatment of Hypertension with Ganglionic Blocking Agents and Hydrazinophthalazine. S. Bjoerk and B. Hood, Uppsala, Sweden.

Rheumatic and Febrile Syndrome Incident to Treatment with Hydralazine. Harriet P. Dustan, Robert D. Taylor, Arthur C. Corcoran and Irvine H. Page, Cleveland.

ROOM C. Congenital Heart Disease, II

Pulmonary Diastolic Murmurs in Congenital Heart Disease. Arnold L. Johnson and Charlotte Ferencz, Montreal.

Clinical and Hemodynamic Observations in Lutembacher's Syndrome. Elliot Rapaport, Murray Rabinowitz, Florence W. Haynes, Hiroshi Kuida and Lewis Dexter, Boston.

Atrial Septal Defect: The Clinical and Hemodynamic Response to Complete Closure. S. Gilbert Blount, Jr., Edwin M. Coyette and Henry Swan, Denver.

The Diagnosis of the Ventricular Septal Defect. John D. Keith, Ontario.

Hemodynamic Studies Following Closure of Atrial

Septal Defects. H. Goldberg and D. Downing, Philadelphia.

Five to Eight Year Follow-Up on the First 500 Blalock-Taussig Operations. Benjamin D. White, Dan G. McNamara, S. Richard Bauersfeld and Helen B. Taussig, Baltimore.

Physiological Studies in Cases of "Tetralogy of Fallot" with Little or no Overriding of the Aorta. C. G. R. Sell, R. L. Fowler, E. Sailors, A. L. Hyman, L. Levy, II and N. K. Ordway New Orleans.

Results of Valvulotomy for Valvular Pulmonary Stenosis with Intact Ventricular Septum (Analysis of 78 Patients). Don M. Hosier, John L. Pitts and Helen B. Taussig, Baltimore.

ROOM 12W. Heart Diseases of Uncommon Etiology, II

Cardiovascular Allergy. Joseph Harkavy, New York.

Dissecting Aneurism Produced by Diet: Some Relations to Arachnodactyly and Kyphoscoliosis. William B. Bean and I. V. Ponseti, Iowa City.

"Familial Myocardosis": A Review of Four Cases. Jorge Soberon Acevedo, Rafael Jose Neri, Antonio Cepeda de la Pena and Luis Saenz Arroyo, Mexico City.

An Integrated Study of Chronic Chagas' Disease (American Trypanosomiasis). Blas Moia, M. B. Rosenbaum and A. J. Alvarez, Buenos Aires.

Research on the Circulation in Osteitis Deformans (Paget's Disease). J. Lequime and H. Denolin, Brussels.

Post-Partum Congestive Heart Failure. Aaron B. Benchimol and Paul Schlesinger, Rio de Janeiro.

The Effects of Chronic Anemia on the Cardiovascular System. Harper K. Hellems and Leonard Leight, Detroit.

Thyrotoxicosis as the Sole Etiologic Factor of Heart Disease. Paul Schlesinger and Aaron B. Benchimol, Rio de Janeiro.

ROOM 27E. Phonocardiography and Auscultation

Spectral Phonocardiography. Victor A. McKusick, George N. Webb, James R. Brayshaw and Samuel A. Talbot, Baltimore.

The First Heart Sound in Mitral Stenosis: A Phonocardiographic Study. Bernardo L. Fishleder, Charlotte Friedland and Gustavo Medrano, Mexico City.

Two Varieties of Reduplication of the Second Sound. C. Lian, Paris.

The Added Sound in Early Diastole in Constrictive Pericarditis. John Patrick David Mounsey, London.

The Opening Snap of the Tricuspid Valve: A Previously Unrecognized Physical Sign of Tricuspid Stenosis. Charles E. Kossmann, New York.

Phonocardiographic Study of Variations in the Diastolic Murmur of Mitral Stenosis. Patrick A. Ongley, Maurice B. Rappaport and Howard B. Sprague, Boston.

Phonocardiography in the Differentiation of Predominant Mitral Regurgitation from Predominant Mitral Stenosis. Peter T. Kuo and Truman G. Schnable, Jr., Philadelphia.

The Action of Human Mitral and Aortic Valves Studied Post-Mortem by Cinematography (Motion Picture). I. K. R. McMillan and R. Daley, London.

FRIDAY MORNING SEPTEMBER 17

Main Auditorium, Room A

SESSION I: 9:00–10:30 A.M.

Symposium: Coronary Heart Disease
Chairman: Howard B. Sprague, Boston
Co-Chairman: Ramon Aixala, Havana

Diet and Coronary Disease. Ancel Keys, Minneapolis.

Experimental Studies of Atherosclerosis. George V. Mann, Boston.

Diagnosis of Coronary Heart Disease. D. Evan Bedford, London.

Treatment of Coronary Heart Disease. Robert L. Levy, New York.

Anticoagulants in Myocardial Infarction. Irving S. Wright, New York.

Anticoagulant Therapy in Myocardial Infarction. Jean Lenegre, Paris.

Treatment of Shock in Threatened and Established Myocardial Infarction. E. Cowles Andrus, Baltimore.

INTERMISSION: 10:30–11:00 A.M.

SESSION II: 11:00–12:00 noon

Charles Laubry Lecture
Leadership in Cardiology.
Sir John Parkinson, London.

12:00–12:30 P.M.

Closing Remarks:
Charles Laubry, Paris.
Paul D. White, Boston.

Simultaneous Scientific Sessions

ROOM B. Subacute Bacterial Endocarditis

Bacterial Endocarditis: An Analysis of 52 Cases. Walter Newman, Jose M. Torres and John Guck, Bronx, New York.

Two New Cases of Bacterial Endocarditis Caused by Klebsiella Pneumoniae (Friedlander's Bacillus), with Successful Treatment of One Patient. James W. Culbertson and Masa Yamamoto, Iowa City.

Rheumatic Fever and Subacute Bacterial Endocarditis. Teodoro Cesarman, Guillermo Ibarra Ibarra, Rosario Barroso-Moguel and Mario Salazar Mallen, Mexico City.

Therapeutic Resistance in Subacute Bacterial Endocarditis. L. Trias De Bes, Barcelona.

Report on a Case of Subacute Bacterial Endocarditis Due to Streptococcus Viridans Resistant to Many Antibiotics but Sensitive to Erythromycin. Rafael . Alzamora-Freundt, Aurelio Peralta, Roberto Delgada V., Pedro Moyano, Marcos Roitman, Carlos Solis, Rafael Reyna and Julio Morales S., Lima, Peru.

Heart Failure as an Early Symptom of Subacute Bacterial Endocarditis. P. Broustet, R. Castaing, P. Blanchot and H. Bricaud, Paris.

Fibroplastic Endocarditis with Eosinophilia (Loeffler's Endocarditis Parietalis Fibroplastica): Case Report and Review of Literature. Franklin G. Hoffman, P. D. Genovese and David Rosenbaum, Geneva, New York.

Virus Endocarditis. Harold Cookson, Bournemouth, England.

ROOM C. Diagnostic and Therapeutic Instruments (First Half A.M.)

The Allard-Laurens Intracardiac Micromanometer. P. Soulie, P. Laurens, E. Allard and F. Bouchard, Paris.

The Left Auricular Oesophageal Piezocardiogram in the Diagnosis of Mitral Lesions. Robison Roubach, A. de Carvalho Azevedo, A. Ney Toledo and A. Alves de Carvalho, Rio de Janeiro.

Stokes-Adams Disease: Its Treatment with an External Electric Cardiac Pacemaker. P. Zoll, A. J. Linenthal, L. R. Norman and Milton H. Paul, Boston.

Direct Writing Phonocardiography. Klaus Holldack, Heidelberg.

Pathology (Second Half A.M.)

Untreated Syphilis in the Male Negro: Pathologic Findings in Syphilitic and Nonsyphilitic Patients. Jesse J. Peters, James H. Peers, Sidney Olansky, John C. Cutler and Geraldine A. Gleeson, Washington, D. C.

Reticulo-Cardiopathies of Parasitic Origin. Ramon A. Rojas and Danio Deza Cenget, Buenos Aires.

Histological Study of Right Bundle Branch Block (Based on 48 Cases). Jean Lenegre, Paris.

Pathological Changes in the Liver in Congestive Heart Failure. Oglesby Paul, Gordon F. Vawter, Albert Schweitzer, George M. Hass and Armin F. Schick, Chicago.

ROOM 12W. Epidemiology

Incidence of Heart Disease in Guatemala: Preliminary Study. Jorge A. Fernandez Mendia, Guatemala, City.

The Pathology of Endomyocardial Fibrosis J. N. P. Davies, Kampala, Uganda, East Africa.

The Problems of Hypertension in Pakistan. Roeinton B. Khambatta, Karachi, Pakistan.

Myocardial Infarction: A Summary of the Findings in the San Jose Ward of the Dos de Mayo Hospital, Lima, Peru During 1937–1952. Marcos Roitman and Jorge A. Orihuela, Lima, Peru.

ROOM 27E. X-Ray and Angiocardiography

Anomalous Drainage of Pulmonary Veins: Clinical, Physiologic and Angiocardiographic Features. Israel Steinberg, Gonzalo Sepulveda and Daniel S. Lukas, New York.

The Roentgenological Diagnosis of Pulmonary Hypertension in Mitral Stenosis. John B. Schwedel, Dennison Young, Doris W. Escher and Robert Aaron, New York.

Pulmonary Circulation in Cardiac and Respiratory Diseases as Studied by Selective Pulmonary Angiography. W. Bolt, H. W. Knipping and H. Rink, Cologne.

X-Ray Symptoms of the Left Atrium. Narno Dorbecker and Susano Aranda, Mexico City.

Visualization of Intracardiac Calcification by Planigraphy. Jacob Zatuchni, Louis A. Soloff and Herbert Fisher, Philadelphia.

A Study of the Correlation between Roentgenographic and Post-Mortem Calcification of the Aorta. Julian B. Hyman and Frederick H. Epstein, New York.

Timed Angiographic Studies in the Peripheral Vessels and Pulmonic and Systemic Circulation in Children. J. Lind, R. Spencer and C. Wegelius, Stockholm.

Angiocardiography in Tricuspid Valve Disease. Pier Federico Angelino and Angelo Actis-Dato, Torino.

Angiocardiography in Mitral Stenosis. Marsh McCall, Lucille Yuen and Lester Blum, New York.

Patent Ductus Arteriosus: A Critical Evaluation of Its Roentgen Signs. Theodore E. Keats and Howard L. Steinbach, San Francisco.

Registration and Fees

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Septal Defects. H. Goldberg and D. Downing, Philadelphia.

Five to Eight Year Follow-Up on the First 500 Blalock-Taussig Operations. Benjamin D. White, Dan G. McNamara, S. Richard Bauersfeld and Helen B. Taussig, Baltimore.

Physiological Studies in Cases of "Tetralogy of Fallot" with Little or no Overriding of the Aorta. C. G. R. Sell, R. L. Fowler, E. Sailors, A. L. Hyman, L. Levy, II and N. K. Ordway New Orleans.

Results of Valvulotomy for Valvular Pulmonary Stenosis with Intact Ventricular Septum (Analysis of 78 Patients). Don M. Hosier, John L. Pitts and Helen B. Taussig, Baltimore.

ROOM 12W. Heart Diseases of Uncommon Etiology, II

Cardiovascular Allergy. Joseph Harkavy, New York.

Dissecting Aneurism Produced by Diet: Some Relations to Arachnodactyly and Kyphoscoliosis. William B. Bean and I. V. Ponseti, Iowa City.

"Familial Myocardosis": A Review of Four Cases. Jorge Soberon Acevedo, Rafael Jose Neri, Antonio Cepeda de la Pena and Luis Saenz Arroyo, Mexico City.

An Integrated Study of Chronic Chagas' Disease (American Trypanosomiasis). Blas Moia, M. B. Rosenbaum and A. J. Alvarez, Buenos Aires.

Research on the Circulation in Osteitis Deformans (Paget's Disease). J. Lequime and H. Denolin, Brussels.

Post-Partum Congestive Heart Failure. Aaron B. Benchimol and Paul Schlesinger, Rio de Janeiro.

The Effects of Chronic Anemia on the Cardiovascular System. Harper K. Hellems and Leonard Leight, Detroit.

Thyrotoxicosis as the Sole Etiologic Factor of Heart Disease. Paul Schlesinger and Aaron B. Benchimol, Rio de Janeiro.

ROOM 27E. Phonocardiography and Auscultation

Spectral Phonocardiography. Victor A. McKusick, George N. Webb, James R. Brayshaw and Samuel A. Talbot, Baltimore.

The First Heart Sound in Mitral Stenosis: A Phonocardiographic Study. Bernardo L. Fishleder, Charlotte Friedland and Gustavo Medrano, Mexico City.

Two Varieties of Reduplication of the Second Sound. C. Lian, Paris.

The Added Sound in Early Diastole in Constrictive Pericarditis. John Patrick David Mounsey, London.

The Opening Snap of the Tricuspid Valve: A Previously Unrecognized Physical Sign of Tricuspid Stenosis. Charles E. Kossmann, New York.

Phonocardiographic Study of Variations in the Diastolic Murmur of Mitral Stenosis. Patrick A. Ongley, Maurice B. Rappaport and Howard B. Sprague, Boston.

Phonocardiography in the Differentiation of Predominant Mitral Regurgitation from Predominant Mitral Stenosis. Peter T. Kuo and Truman G. Schnable, Jr., Philadelphia.

The Action of Human Mitral and Aortic Valves Studied Post-Mortem by Cinematography (Motion Picture). I. K. R. McMillan and R. Daley, London.

FRIDAY MORNING SEPTEMBER 17

Main Auditorium, Room A

SESSION I: 9:00–10:30 A.M.

Symposium: Coronary Heart Disease
Chairman: Howard B. Sprague, Boston
Co-Chairman: Ramon Aizala, Havana

Diet and Coronary Disease. Ancel Keys, Minneapolis.

Experimental Studies of Atherosclerosis. George V. Mann, Boston.

Diagnosis of Coronary Heart Disease. D. Evan Bedford, London.

Treatment of Coronary Heart Disease. Robert L. Levy, New York.

Anticoagulants in Myocardial Infarction. Irving S. Wright, New York.

Anticoagulant Therapy in Myocardial Infarction. Jean Lenegre, Paris.

Treatment of Shock in Threatened and Established Myocardial Infarction. E. Cowles Andrus, Baltimore.

INTERMISSION: 10:30–11:00 A.M.

SESSION II: 11:00–12:00 noon

Charles Laubry Lecture
Leadership in Cardiology.
Sir John Parkinson, London.

12:00–12:30 P.M.

Closing Remarks:
Charles Laubry, Paris.
Paul D. White, Boston.

Simultaneous Scientific Sessions

ROOM B. Subacute Bacterial Endocarditis

Bacterial Endocarditis: An Analysis of 52 Cases. Walter Newman, Jose M. Torres and John Guck, Bronx, New York.

Two New Cases of Bacterial Endocarditis Caused by Klebsiella Pneumoniae (Friedlander's Bacillus), with Successful Treatment of One Patient. James W. Culbertson and Masa Yamamoto, Iowa City.

Rheumatic Fever and Subacute Bacterial Endocarditis. Teodoro Cesarman, Guillermo Ibarra Ibarra, Rosario Barroso-Moguel and Mario Salazar Mallen, Mexico City.

Therapeutic Resistance in Subacute Bacterial Endocarditis. L. Trias De Bes, Barcelona.

Report on a Case of Subacute Bacterial Endocarditis Due to Streptococcus Viridans Resistant to Many Antibiotics but Sensitive to Erythromycin. Rafael Alzamora-Freundt, Aurelio Peralta, Roberto Delgada V., Pedro Moyano, Marcos Roitman, Carlos Solis, Rafael Reyna and Julio Morales S., Lima, Peru.

Heart Failure as an Early Symptom of Subacute Bacterial Endocarditis. P. Broustet, R. Castaing, P. Blanchot and H. Bricaud, Paris.

Fibroplastic Endocarditis with Eosinophilia (Loeffler's Endocarditis Parietalis Fibroplastica): Case Report and Review of Literature. Franklin G. Hoffman, P. D. Genovese and David Rosenbaum, Geneva, New York.

Virus Endocarditis. Harold Cookson, Bournemouth, England.

ROOM C. Diagnostic and Therapeutic Instruments (First Half A.M.)

The Allard-Laurens Intracardiac Micromanometer. P. Soulie, P. Laurens, E. Allard and F. Bouchard, Paris.

The Left Auricular Oesophageal Piezocardiogram in the Diagnosis of Mitral Lesions. Robison Roubach, A. de Carvalho Azevedo, A. Ney Toledo and A. Alves de Carvalho, Rio de Janeiro.

Stokes-Adams Disease: Its Treatment with an External Electric Cardiac Pacemaker. P. Zoll, A. J. Linenthal, L. R. Norman and Milton H. Paul, Boston.

Direct Writing Phonocardiography. Klaus Holldack, Heidelberg.

Pathology (Second Half A.M.)

Untreated Syphilis in the Male Negro: Pathologic Findings in Syphilitic and Nonsyphilitic Patients. Jesse J. Peters, James H. Peers, Sidney Olansky, John C. Cutler and Geraldine A. Gleeson, Washington, D. C.

Reticulo-Cardiopathies of Parasitic Origin. Ramon A. Rojas and Danio Deza Cenget, Buenos Aires.

Histological Study of Right Bundle Branch Block (Based on 48 Cases). Jean Lenegre, Paris.

Pathological Changes in the Liver in Congestive Heart Failure. Oglesby Paul, Gordon F. Vawter, Albert Schweitzer, George M. Hass and Armin F. Schick, Chicago.

ROOM 12W. Epidemiology

Incidence of Heart Disease in Guatemala: Preliminary Study. Jorge A. Fernandez Mendia, Guatemala, City.

The Pathology of Endomyocardial Fibrosis J. N. P. Davies, Kampala, Uganda, East Africa.

The Problems of Hypertension in Pakistan. Roeinton B. Khambatta, Karachi, Pakistan.

Myocardial Infarction: A Summary of the Findings in the San Jose Ward of the Dos de Mayo Hospital, Lima, Peru During 1937–1952. Marcos Roitman and Jorge A. Orihuela, Lima, Peru.

ROOM 27E. X-Ray and Angiocardiography

Anomalous Drainage of Pulmonary Veins: Clinical, Physiologic and Angiocardiographic Features. Israel Steinberg, Gonzalo Sepulveda and Daniel S. Lukas, New York.

The Roentgenological Diagnosis of Pulmonary Hypertension in Mitral Stenosis. John B. Schwedel, Dennison Young, Doris W. Escher and Robert Aaron, New York.

Pulmonary Circulation in Cardiac and Respiratory Diseases as Studied by Selective Pulmonary Angiography. W. Bolt, H. W. Knipping and H. Rink, Cologne.

X-Ray Symptoms of the Left Atrium. Narno Dorbecker and Susano Aranda, Mexico City.

Visualization of Intracardiac Calcification by Planigraphy. Jacob Zatuchni, Louis A. Soloff and Herbert Fisher, Philadelphia.

A Study of the Correlation between Roentgenographic and Post-Mortem Calcification of the Aorta. Julian B. Hyman and Frederick H. Epstein, New York.

Timed Angiographic Studies in the Peripheral Vessels and Pulmonic and Systemic Circulation in Children. J. Lind, R. Spencer and C. Wegelius, Stockholm.

Angiocardiography in Tricuspid Valve Disease. Pier Federico Angelino and Angelo Actis-Dato, Torino.

Angiocardiography in Mitral Stenosis. Marsh McCall, Lucille Yuen and Lester Blum, New York.

Patent Ductus Arteriosus: A Critical Evaluation of Its Roentgen Signs. Theodore E. Keats and Howard L. Steinbach, San Francisco.

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Heart Association attending the Annual Scientific Sessions, the heavy expenses entailed by the enlarged and integrated sessions of the forthcoming Congress and the many events associated with an international meeting of this kind require that a fee be charged this year. The $25.00 fee entitles members to attend all scientific sessions, the opening reception, formal banquet and other social events planned for Congress delegates, the exhibits and special sightseeing tours to medical installations in Washington and its environs. Also included are the printed program, directory of registrants, Congressional badge and other items.

Associate membership (wives and family) has been arranged at a cost of $15.00. It will include all privileges mentioned above except the printed program. *A schedule of reduced fees has been provided for limited attendance by physicians and for attendance by such groups as medical students, interns and nurses.*

Exhibits

Scientific and industrial exhibits have been planned for the Congress, as well as a motion picture program of professional and scientific films on cardiovascular subjects.

SECTION ON CIRCULATION

In addition to presenting the George Brown Lecture of the A.H.A. on Tuesday morning, September 14, at the Second World Congress of Cardiology, and a Tuesday afternoon program, both in the Main Auditorium of the National Guard Armory, the Section on Circulation of the Scientific Council has arranged several special events.

The Executive Committee of the Section on Circulation will hold a dinner meeting on Monday evening, September 13, at the Shoreham Hotel. The Annual Dinner of the Section will be held on Wednesday evening, September 15, also at the Shoreham Hotel. A special Scientific Program will be held on Monday morning, September 13, at 9:30 A.M. The papers to be presented are as follows:

The Pathogenesis of Postural Syncope. Frank A. Finnerty, Jr., Joseph F. Fazekas, Edward A. Partenope, John C. Rose, and Lawrence S. Lilienfield, Washington, D. C.

A Dynamic Model for the Controlled Study of Thrombus Formation. Jerrold S. Lieberman, New York.

The Venous Pressure-Volume Curve of the Human Leg Measured in Vivo. Julius Litter, J. Edwin Wood, and Robert W. Wilkins, Boston.

A New Method for Measuring Simultaneously the Time Course of Digital Rates and Volumes of Inflow, Outflow and Differences between Inflow and Outflow during a Single Pulse Cycle. George E. Burch, New Orleans.

The Chemical Quantitation of Epinephrine and Norepinephrine. William M. Manger, Edward J. Baldes, Eunice V. Flock, Joseph Berkson, Jesse L. Bollman, and Martin Jacobs, Rochester, Minnesota.

SPCA-Induced Thrombosis: Its Pathogenesis and the Effect of Antiocoagulants. Stanford Wessler, Boston.

OTHER SPECIAL MEETINGS

International Society of Cardiology

Council, Mayflower Hotel, Saturday, Sept. 11, 7:30 p.m.

Council, Mayflower Hotel, Sunday, Sept. 12, 5 p.m.

Assembly, National Guard Armory, Monday, Sept. 13, 12:30 p.m.

Assembly, National Guard Armory, Wednesday, Sept. 15, 12:30, p.m.

American Heart Association

Scientific Council, Annual Meeting, National Guard Armory, Wednesday, Sept. 15, 12:30.

Committee on Clinics, Mayflower Hotel, Wednesday, Sept. 15, 3:30–5:30 p.m.

Executive Committee, Section on Clinical Cardiology, Dinner Meeting, Mayflower Hotel, Wednesday, Sept. 15, 7:30 p.m.

Clinical Advisory Committee, Section on Cardiovascular Surgery, Luncheon Meeting, Mayflower Hotel, Thursday, Sept. 16, 1:30.

MEETINGS

Sept. 6: American Society of Clinical Pathologists, Washington, D. C.; C. G. Culbertson, Secretary, 1040 W. Michigan Street, Indianapolis, Ind.

Sept. 6–10: International Congress of Clinical Pathology; Washington, D. C.; Dr. Robert A. Moore, Chairman, Committee on Arrangements, Washington University School of Medicine, St. Louis 10, Mo.

Sept. 9–10: Vermont Heart Association and University of Vermont College of Medicine Seminar on Cardiac Arrhythmias; Burlington, Vt.; E. Lepeschkin, M.D., University of Vermont College of Medicine, Burlington, Vt.

Sept. 11: Vermont Heart Association and University of Vermont College of Medicine Symposium on the U wave of the Electrocardiogram; Burlington, Vt.; E. Lepeschkin, M.D., University of Vermont College of Medicine, Burlington, Vt.

Sept. 26–Oct. 2: World Medical Association; Rome, Italy; Louis H. Bauer, Secretary, 345 East 46th Street, New York 17, N. Y.

Oct. 22–23: Annual Meeting and Scientific Program, Council for High Blood Pressure Research, American Heart Association, Cleveland; Irving S. Wright, M.D., Chairman, Program Committee, % American Heart Association, 44 East 23rd St., New York 10.

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CONTENTS

ISOLATED VALVULAR PULMONIC STENOSIS. CLINICAL AND PHYSIOLOGIC RESPONSE TO OPEN VALVULOPLASTY
S. Gilbert Blount, Jr., Malcolm C. McCord, Helmut Mueller, and Henry Swan 161

ANTIBIOTIC THERAPY OF BACTERIAL ENDOCARDITIS. VI. SUBACUTE ENTEROCOCCAL ENDOCARDITIS: CLINICAL, PATHOLOGIC AND THERAPEUTIC CONSIDERATION OF 33 CASES ..... *Joseph E. Geraci and William J. Martin* 173

THE DYNAMICS OF THE HEART IN COMPLETE A-V BLOCK. AN ANGIOCARDIOGRAPHIC STUDY ..... *John Lind, Carl Wegelius, and Henrik Lichtenstein* 195

LOWERING OF SERUM CHOLESTEROL BY THE ADMINISTRATION OF A PLANT STEROL
Maurice M. Best, Charles H. Duncan, Edward J. Van Loon, and Joan D. Wathen 201

THE CLINICAL DETERMINATION OF MITRAL INSUFFICIENCY WHEN ASSOCIATED WITH MITRAL STENOSIS ..... *O. Henry Janton, Guenther Heidorn, Louis A. Soloff, Thomas J. E. O'Neill, and Robert P. Glover* 207

ANTICOAGULANT THERAPY WITH DICUMAROL MAINTAINED DURING MAJOR SURGERY ..... *Sten Müllertz and Ole Storm* 213

ATRIAL RUPTURE OF THE HEART. REPORT OF CASE FOLLOWING ATRIAL INFARCTION AND SUMMARY OF 79 CASES COLLECTED FROM THE LITERATURE
Robert M. Kohn, Raymond Harris, and L. Whittington Gorham 221

PERSISTENT SUPRAVENTRICULAR TACHYCARDIA. CASE REPORT WITH REVIEW OF LITERATURE ..... *Norman Shachnow, Stanley Spellman, and Ira Rubin* 232

EFFECTS OF CORTISONE, HYDROCORTISONE AND CORTICOTROPIN ON LIPEMIA, GLYCEMIA AND ATHEROGENESIS IN CHOLESTEROL-FED CHICKS
Jeremiah Stamler, Ruth Pick, and Louis N. Katz 237

ESTROGEN PROPHYLAXIS OF CHOLESTEROL-INDUCED CORONARY ATHEROGENESIS IN CHICKS GIVEN ADRENAL CORTICOIDS OR ACTH
Jeremiah Stamler, Ruth Pick, and Louis N. Katz 247

INHIBITION OF CHOLESTEROL-INDUCED CORONARY ATHEROGENESIS IN THE EGG-PRODUCING HEN ..... *Jeremiah Stamler, Ruth Pick, and Louis N. Katz* 251

PROLONGED OBSERVATIONS OF THE CARDIOVASCULAR STATUS IN ESSENTIAL HYPERLIPEMIA: WITH SPECIAL REFERENCE TO SERUM LIPID RESPONSE TO HEPARIN
Alfred Soffer and Martin Murray 255

A COMPARISON OF THE CEREBRAL HEMODYNAMIC RESPONSE TO ARAMINE AND NOREPINEPHRINE IN THE NORMOTENSIVE AND THE HYPOTENSIVE SUBJECT
John H. Moyer, George Morris, and Harvey Snyder 265

THE RELATION BETWEEN BLOOD ORGANIC ACID SOLUBLE PHOSPHATE FRACTIONS, CITRIC ACID, PROTEIN FRACTIONS, AND LIPID FRACTIONS IN ATHEROSCLEROTIC HEART DISEASES AND IN LIPEMIAS
Sidney P. Gottfried, Nathan H. Friedman, Irving B. Akerson, Russell H. Pope, and Salvatore Di Mauro 271

CLINICAL METHOD OF PHOTOGRAPHING THE SMALLER BLOOD VESSELS AND THE CIRCULATING BLOOD IN THE BULBAR CONJUNCTIVA OF HUMAN SUBJECTS
Jørn Ditzel, and Richard W. St. Clair 277

CLINICAL PROGRESS. SYNDROME OF SHORT P-R INTERVAL WITH ABNORMAL QRS COMPLEXES AND PAROXYSMAL TACHYCARDIA (WOLFF-PARKINSON-WHITE SYNDROME) ..... *Louis Wolff* 282

ABSTRACTS 292

AMERICAN HEART ASSOCIATION 308